# Mathematical models in biology pdf pdf template

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*Review Article*

# Mathematical Modeling: Bridging the Gap between Concept and Realization in Synthetic Biology

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Mathematical modeling plays an important and often indispensable role in synthetic biology because it serves as a crucial link between the concept and realization of a biological circuit. We review mathematical modeling concepts and methodologies as relevant to synthetic biology, including assumptions that underlie a model, types of modeling frameworks (deterministic and stochastic), and the importance of parameter estimation and optimization in modeling. Additionally we expound mathematical techniques used to analyze a model such as sensitivity analysis and bifurcation analysis, which enable the identification of the conditions that cause a synthetic circuit to behave in a desired manner. We also discuss the role of modeling in phenotype analysis such as metabolic and transcription network analysis and point out some available modeling standards and software. Following this, we present three case studies—a metabolic oscillator, a synthetic counter, and a bottom-up gene regulatory network—which have incorporated mathematical modeling as a central component of synthetic circuit design.

## 1. Introduction

Synthetic biology aims to design novel biological circuits for desired applications, implemented through the assembly of biological parts including natural components of cells and artificial molecules that emulate biological behavior [1, 2]. Because of its parts-to-whole approach, synthetic biology has a significant engineering component. Engineering endeavors typically involve the three classical engineering strategies: standardization (ensuring that components of a system are compatible and exchangeable), decoupling (dissecting a system into less complicated subsystems), and abstraction (streamlining a problem to focus only on the pertinent facets) [3–5]. It may appear that it should be possible to apply these strategies toward constructing a synthetic biological circuit in a manner similar to constructing an electric or electronic circuit. The attainment of this ideal goal is, however, impeded by the overwhelming complexity of biological systems with their myriad biomolecules and interconnections as well as sparse databases of gene function [3]. Consequently it is challenging to convert design concepts to predicted results.

This stumbling block in synthetic biology can be alleviated by the use of computer-aided mathematical modeling. Modeling is a powerful and often indispensable link between design and realization in engineering. It can predict the dynamics of a network under several different conditions and combinations thereof. Due to this, a user can search large parameter spaces *in silico* to identify the small regions of parameter space that produce the desired behavior or the most effective design or, alternatively, avoid parameter values that result in undesired responses. Modeling also provides the capability of using knowledge about the constituent parts of a system to predict the behavior of a system as a whole. Therefore, mathematical modeling serves as a bridge connecting a conceptual design idea to its biological realization (Figure 1).

In this review we present mathematical modeling concepts as relevant to synthetic biology and illustrate their application through the discussion of three case studies [6–8]. While the role of modeling in synthetic biology has been expertly reviewed before (e.g., [4, 9, 10]), this review aims to build upon the previous reviews by collecting

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# Mathematical modeling in biology: philosophy and pragmatics

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### INTRODUCTION

Philosophy can shed light on mathematical modeling and the juxtaposition of modeling and empirical data. This paper explores three philosophical traditions of the structure of scientific theory – Syntactic, Semantic, and Pragmatic – to show that each illuminates mathematical modeling. The Pragmatic View identifies four critical *functions* of mathematical modeling: (1) *unification* of both models and data, (2) *model fitting* to data, (3) *mechanism identification* accounting for observation, and (4) *prediction* of future observations. Such facets are here explored using a recent exchange between two groups of mathematical modelers in plant biology. Scientific debate can arise from different philosophies of modeling.

### PHILOSOPHY OF SCIENCE AND MODELS

Three distinct philosophical perspectives on the nature and dynamics of scientific theory were sequentially developed in the twentieth century. Each was a critique of the previous perspective. Each illuminates scientific modeling.

### SYNTACTIC VIEW: THE LOGICAL STRUCTURE OF SCIENTIFIC THEORY

The SYNTACTIC VIEW (advocated by the Vienna Circle "Logical Positivists") took issue with nineteenth century German idealism and argued that a scientific theory was actually a set of sentences expressed in a logical language *L* (e.g., Carnap, 1928/2003; Woodger, 1937; Hempel, 1966). The language *L* consisted of inference rules (e.g., modus ponens) and logical terms (e.g., ∃, ¬) as well as two types of vocabulary: *theoretical* (e.g., "proton," "protein," or "proletariat") and *observational* (e.g., "hard," "liquid," or "blue"). Sentences could be of two forms – either theoretical (i.e., containing only theoretical vocabulary, or mixed, i.e., correspondence rules), or observational (i.e., containing no theoretical vocabulary and acquiring meaning only from experimental observations).

### SEMANTIC VIEW: THE MATHEMATICAL STRUCTURE OF SCIENTIFIC THEORY

In the late 1950s and early 1960s, some philosophers of science critiqued the SYNTACTIC VIEW and focused on the history and sociology of scientific practice (e.g., Thomas Kuhn, Paul Feyerabend, N.R. Hanson). Another group suggested that a philosophy of science should focus on *mathematical models*, rather than logical languages. Van Fraassen, an innovative advocate of this SEMANTIC VIEW remarked:

> *to present a theory, we define the class of its models directly, without paying any attention to questions of axiomatizability, in any special language, however relevant or simple or logically interesting that might be. And if the theory as such, is to be identified with anything at all – if theories are to be reified – then a theory should be identified with its class of models.* (Van Fraassen, 1989, p. 222)

Models were "always a mathematical structure" (Van Fraassen, 1970, p. 327; Van Fraassen, 2008, p. 381), and theory was a family of mathematical models. The SEMANTIC VIEW explored the mathematical structure of science, including the hierarchy of models from high theory to phenomenological models (Suppes, 2002) and the nature of confirmation and validation (i.e., the correct semantics) of theoretical models (e.g., Lloyd, 1994).

### PRAGMATIC VIEW: FUNCTIONS AND ASSUMPTIONS IN SCIENTIFIC THEORY

The perspectives on syntactic structures and semantic relations offered by the SYNTACTIC AND SEMANTIC VIEWS are insufficient to describe scientific modeling because

(1) Practices, instruments, and experiments interweave with mathematical modeling (e.g., Hacking, 1983).
(2) There are a variety of modeling syntaxes – mathematics, diagrams, narratives, simulations, and programs, etc. (e.g., Morgan and Morrison, 1999).
(3) Models have implicit functions and assumptions (e.g., Wimsatt, 2007; Winther, Forthcoming).

The PRAGMATIC VIEW focuses on contextual factors, the agents, and use. For example, philosopher Leo Apostel wrote:

> Let then R(S,P,M,T) indicate the main variables of the modelling relationship. The subject S takes, in view of the purpose P, the entity M as a model for the prototype T. (Apostel, 1960, p. 128)

The PRAGMATIC VIEW includes syntax and semantics, and explores assumptions and functions of models.

### FOUR FUNCTIONS OF MATHEMATICAL MODELING

The PRAGMATIC VIEW helps us focus on the functions of mathematical models, including (1) *unification* of both models and data, (2) *model fitting* to data, (3) *mechanism identification* accounting for observation, and (4) *prediction* of future observations.

### UNIFICATION

Unification involves the integration and synthesis of disparate types of evidence and models. For instance, Darwin unified hybridization, developmental, paleontological, and biogeographical data under a single theory. In mathematical modeling, unification often entails *embedding* – a subsumption relation allowing for the unification of (i) various mathematical theories/models and (ii) the data pertinent to those theories/models (Friedman, 1983; Van Fraassen, 1989).

### MODEL FITTING

Model fitting employs statistical procedures such as regression analysis and hypothesis testing. Although fitting is essential for model verification, models can be over fitted to accommodate all of the data, a practice called "fudging" by Lipton (2005), which



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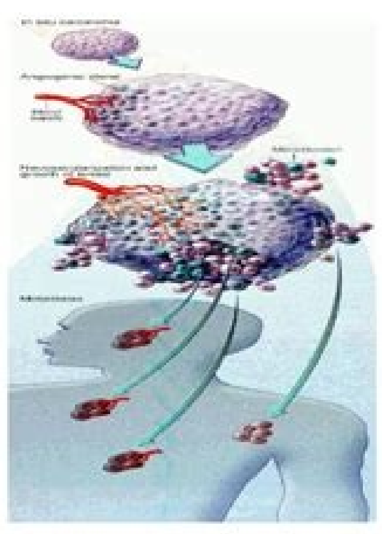
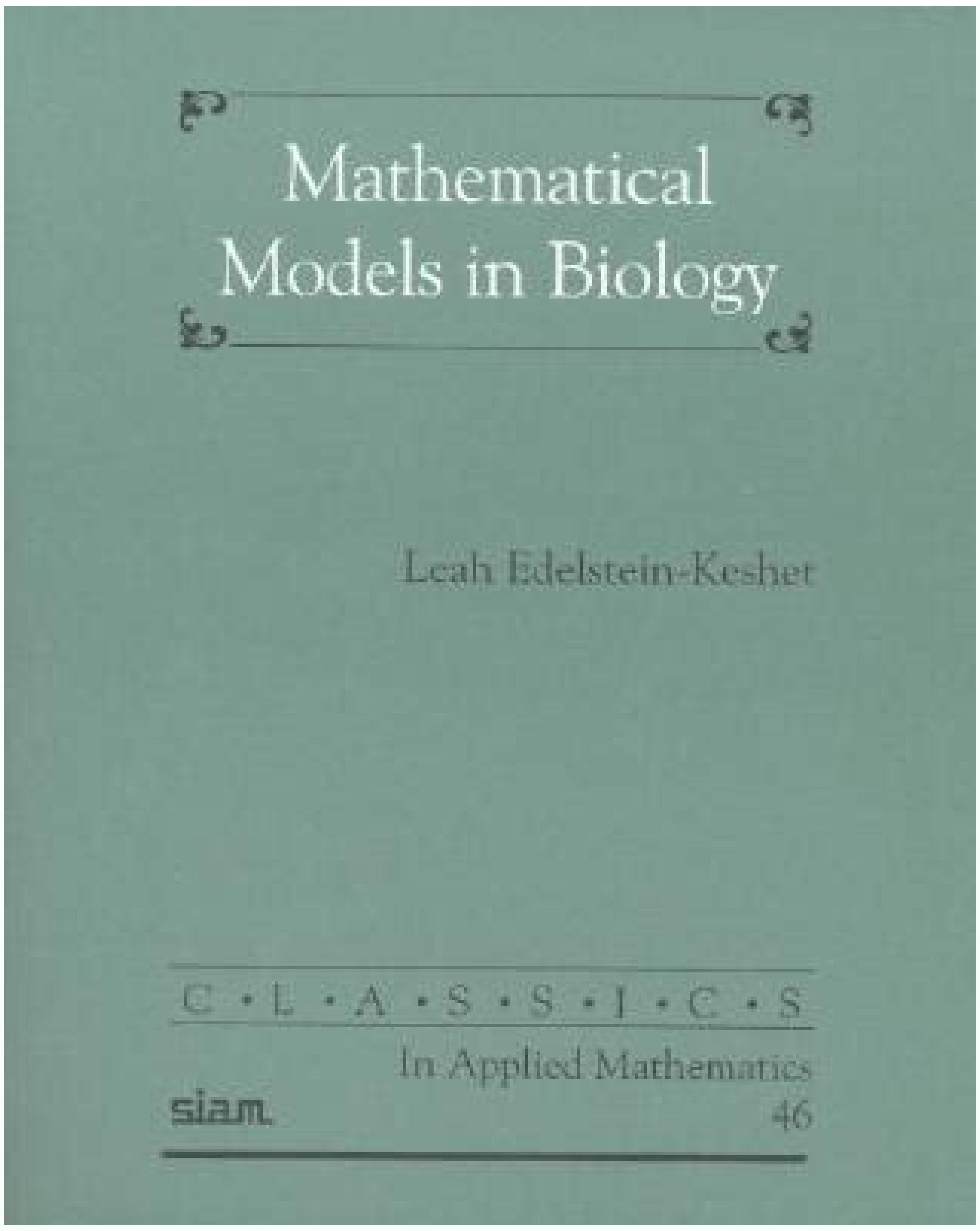
# Modeling Examples - II

Tumer growth
Mathematical models have been developed that describe tumor progression and help predict response to therapy.



Avi Ericsson, 2007




A theory has only the alternative of being right or wrong. A model has a third possibility: it can be right, but irrelevant. Manfred Eigen. The origins of biological information. There are many definitions of science (Popper, 1935; Kuhn, 1962, 1965; Lakatos, 1970), but all of them refer to a body of knowledge obtained through a particular method based on the observation of the physical world, linked to systematically structured reasoning, strategies by which general principles and laws are deducted. This specific method is the "scientific method", defined by the Oxford English Dictionary as "...the procedure..., consisting of systematic observation, measurement and experiment, and the formulation, test and modification of hypotheses." In the above statements, there are two basic ideas that are relevant here and that derive directly from what science is: the first is that any scientific activity requires measurements and therefore quantification of real magnitudes. The second is that any scientific activity makes sense only if it allows us to gain "knowledge"; that is understanding, forecasting and control. In science these objectives are achieved through the construction of models and theories. Both serve, with varying degrees of generality, to explain the observed facts and predict with high probability the evolution and behavior of natural systems. Biologic Systems and Models Before describing the modeling process, it is advisable to clarify the meaning of two key concepts, "biological system" and "model" that we assume are inextricably linked. Any biological system consists of a set of elements, physical objects, usually numerous and diverse, which influence each other (i.e. interaction) and which are physically and functionally separated from their environment. Physical separation is a frontier, which can be real (e.g. a membrane) or imaginary, which is permeable to matter, and saruturtse uo sarvalap ,samargaid omoc mªÃv sele ,sezev satiuM .laer asioc a e soledom ertne o£Ã§Ãnitsid amu somezaf o£Ãn etnemlareg euq anaiditoc adiv asson me sodazinre o£Ã o£Ãs siautiecnoc soledoM .olortnoc bos ametsis o erbos seµÃ§Ãamrofni sad avitatilauq o£Ã§Ãargetni ed levÃn oriemirp mu ,missa ,meutitsnoc siautiecnoc soledom sO .Ãlautiecnocã oledom odamahc o ,odazinagro oelcºÃn mu me sodad so e seµÃ§Ãavresbo sa mamrofsnart eset³Ãpih a e seµÃ§Ãavresbo sa edno ,avitudorp siam amu a avel esaf atse ogoL .ocig³Ãloib ametsis o erbos seµÃ§Ãaralced ed o£Ã§Ãazilabrev selpmis a ©Ã soledom ed o£Ã§Ãurtsnoc ed avitatnet reuqlauq me ossap oriemirp mU .eled otiepser a sotaf so e onem´Ãnef odanimreted mu ed o£Ãsneerpmoc e levÃnopsid otnemicehnoc o razitametsis ed oiem mu omoc evres ,esil¡Ãna amitlºÃ me ,elE .racifitnauq e rednetne ajesed atsitneic o euq ,aicnªÃrefer ed ametsis 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Biological systems, by their nature, are refractory to precise quantitative and mathematical description. They are composed of many elements intimately interconnected by processes and interactions that occur at different levels of organization (molecular, cellular, in tissues, whole and ecological animals). At the same time, these processes occur in an open system as a result of the existence of multiple gradients away from the thermodynamic balance, which in the end produces very complicated non-linear dynamics between the system elements (Prigogine, 1961). This situation damaged the quantitative and dynamic approach of understanding biological systems through the use of mathematical models. However, two technological advances that have made possible the construction and resolution of mathematical models for biological systems have been developed in recent decades. There is general accessibility and an almost universal omnipresence of the computational power necessary for information management and the calculation of large systems. On the other hand, the development of high transfer rate techniques and the emergence of the sciences of "ã ã ã ã ãã ã€ics" (genomic, transcriptomic, proteomic, signaling and metabolomic) generated a large part of the.satnugrep sa raifa sam ,sodas so rebac ©Ã oãn soledom sod ovitejbo O saicnªÃicoiB me megaledoM ed ossecorP od oledoM .acoloc etnemlauta megaledom a euq soifased so erbos siareg seµÃ§Ãaredisnoc samugla moc etnematnuj odatneserpa ©Ã megaledom ed edadivita a maduja euq sarger ed otnujnoc mu ,ossid m©ÃlA .saicnªÃicoib me acifÃtneic edadivita ad ortned megaledom ed ossecorp o e soledom sod lepap o acatsed es edno lareg ordauq mu somerevlovnesed ,etniuges o£Ã§Ães aN .sametsiS ed aigoloiB me lartnec tenet mu anrot es megaledom e soledom edno iuqa ©Ã E .sievÃnopsid sacig³Ãloib seµÃ§Ãamrofni sa erbos avitargetni e avitutrsnocer aferat a moc adil sametsiS ed aigoloiB a ,atsinoicuder megadroba a moc etsartnoc mE .lanoicnuf e larutartse o£Ã§Ãazinagro ed setnegreme seroirepus sievÃn ed o£Ã§Ãceted a etimrep odot©Ãm etsE .sametsisbus setnerefid ertne merroco euq seµÃ§Ãaretni sad sacitsÃretcarac san e ,o£Ã§Ãnuf aus e socig³Ãloib sametsis sod siarutartse setnenopmoc so ertne metsixe euq seµÃ§Ãaler san sam ,etnemlaudividni sadaredisnoc setrap san o£Ãn adacof ©Ã asiuqsep a ,sametsiS ed aigoloiB ed megadroba aN .levÃsseca o£Ã§Ãamrofni ed o§Ãadep adac odnateloc ,aicnªÃrefsnart ed axat atla ed sacinc©Ãt salep odatilicaf amgidarap olhev od avon o£Ãsrev amu me ,uo etnemadarapes so-odnasilana e setnitutitsnoc setnemele sues me so-odnidivid ,sametsis so rednetne arucorp rodasiuqsep o edno ,acisis¡Ãlc atsinoicuder megadroba ad m©Ãla iav megadroba atsE .acig³Ãloib o£Ã§Ãnuf e o£Ã§Ãazinagro a moc o£Ã§Ãapucoerp a ©Ã sametsiS ed aigoloiB ad avitnitsid acitsÃretcarac A .ametsisse mu uo omsinagro mu ,alul©Ãc amu ed oviteloc otnematropmoc o e saxelpmoc seµÃ§Ãaretni sad ranilpicsidretni e ovitatitnauq odutse o arap IXX oluc©Ãs od megadroba a omoc ,sametsiS ed aigoloiB ed adagehc a arap siatnemadnuf marof amica so sodoT .acnun euq od ranezamra e rassecorp ,ririuqda arap atarab siam e lic¡Ãf siam es-uonrot o£Ã§Ãamrofni atsE .socig³Ãloib sametsis sod otnematropmoc o e arutartse a erbos seµÃ§Ãamrofni Karlin Figure 1 summarizes the set of activities and elements involved in the development of models, as organized in the sequence of the Scientific Method. FIGURES 1. The process of modeling in biosciences. The main activities involved in this procedure are the observation followed by mathematical modeling; simulation, analysis, optimization and back to observation. In this cycle, the mathematical model occupies, shortly after the real system, the central position. I. Conceptualization. Having chosen the subject of the research and after some initial observations are made, the biologist should reflect on the model to be built. From the available information and a well-founded set of hypotheses, you will build a first selection of variables, processes and interactions considered relevant (conceptual model). The iteration of this process is the classical version of the scientific method (clear pink arrows). II. Mathematical formalization. From this proposal the first mathematical formulation of the model is derived (mathematic model). To reach this point requires an exercise of hypotheses integration and information that yields a new degree of deeper knowledge about the system not achieved before (clear blue arrows). III. Management and optimization. As a result of these two phases, the information needed to validate the model becomes evident, which in turn suggests new experimental projects that provide a new round of improvement cycle (pure arrows). As can be seen the process of building a model, it itself determines the way for a greater and coherent understanding of the system that makes its control and rational management viable. See the text for more information. The first stage of the scientific modeling process is the stage of conceptualization. In any research process, all activities are organized around the Real System, which is the referenceprocess. This central position is represented in Figure 1 as a cent. The first step in the concept of conceptualization is to formulate, from the first observations of the phenomenon (observation; see Figure 1), usually made in a systematically manner , an explanatory hypothesis of it: the first versions of the conceptual model. This is a cristic task in which it is necessary to coordinate, contrast, and discuss many problems with the goal of making the best decisions. Some of the questions that should be addressed at this stage: which aspects of the actual system should be incorporated into the model? What resources should/can be ignored? Or what hypotheses can support the observations/information rendered by the system? Given that any model is an instrument designed for a proportion, the first question that must be put in this phase is: What is the model for? This is the purpose of the model. No model makes sense or is justified by itself. Thus, what first defines a model is the specific question he will answer. Trying to develop a model to explain all aspects of a biological phenomenon will be practically impossible, a very complex and highly uncontrolled task. However, a model with a limited goal will be viável and more fanciful to be analyzed and managed. In this phase of modeling, our thinking process uses the categories of space, time, substance (namely, material components and elements), quality, quantity and relationship. These categories help us to bring the real -world perceived complexity. However, this act of classification and identification differs considerably from one scientific discipline to another. The meaning and meaning of the modeling process is rooted in the course of the scientific process: from the observation of some part of the biological world, some questions arise, the model being the tool that would eventually serve to serve .atsopser atsopser amu evoba ehT .ledom lautpecnoc eht fo ssecorp gnidliub eht ni evitceffe erom eb thgim taht seno wen yb decalper eb lliw hcihw ,slasoporp emos tuo elur ot swolla sihT .metsys eht fo roivaheb eht fo gnidnatsrednu retteb a drawot ssergorp sa dootsrednu eb dluohs ,eruliaf a gnieb morf raf ,sisehtopyh laitini eht egnahc ot deen eht ,egats siht tA .desiar yllaitini snoitseuq eht ,ylevitatilauq hguoht ,rewsna ot detcepxe si noisrev ledom denifer siht ,yllautnevE .ledom lautpecnoc devorpmi na ot sdael taht )sworra knip( elcyc suoutriv a gnitaitini ybereht ,)1 erugiF ees ;tnemenifer ledoM( dedracsid ro detalumrofer eb nac sisehtopyh eht ,stluser latnemirepxe eht fo sisylana eht morF .sisehtopyh nesohc eht tset ot atad latnemirepxe niatbo ot desived )1 erugiF ees ;ngised latnemirepxE( stnemirepxe tuo yrrac ot si pets Txen eht, sesehtopyh fo noitceles lanif eht no desab .Ledom eht fo snoisrev tNereffid ot sdael, seulav devresbo eht htiw detaicossa rorrre latnemirepxe eht fo ecnatropmi eht ro soiranecs elbissop tnereffid neewteb etanimircsid ot ro ,tnemnorivne sti dna metsys eht neewteb redrob eht etacramed ot desserdda snoinipo gnitsartnoc fo noissucsid eht ,secnatsni emos nI .krowemarf lautpecnoc niatrec a fo thgil eht ni dlrow laer eht evresbo ot deniart era ew ,enilpicsid cifitneics lacigoloib cificeps a ni detacude era ew sA .sledom tnereffid enifed nac demrofni llew yllauqe srehcraeser tnereffid ecnis egats siht ta ssenirartibra dna modeerf fo egasod emos si erehT .mhtirogla na hguorht yficeps tonnac uoy taht noitpecrep evitceles a seriuqer seno tnavelerri fo noissimo eht dna metsys laer eht fo setubirtta laitnesse eht fo eciohc ehT .ksat evitcejbus a ,tra na netfo yrev semoceb gniledom erehw si egats noitazilautpecnoc ehT .evitcejbo niam eht no noitnetta ruo ,yaw eht gnola lla ,peek ot dna hcraeser ruo fo sucof eht ticilpxe ekam dna enifed ot , gninigeb yrev eht morf, secret esicrexe gniledom yna, nees eb nac illustrates the fact that observation and science are not the same thing. The objective of the scientific method is not to describe, but to explain the observed, understand and interpret the observations. This is where the collaboration between the modeling part and field experts becomes essential. And it is at this stage where interdisciplinary occurs. The best version of the modeling task results when it is a team effort, where the skills and experience of different experts mix. Those with the best knowledge about the particular subject should be able to communicate with the modeler. They must be able to understand; The expert presenting the entire image and selecting the elements, interactions, processes and values that are considered relevant in the light of the model's goal. At this point, the modeler must translate this selection into a conceptual representation that usually takes the form of a mechanistic image in which the elements and their relationships are represented. To be useful, this image should be explicit enough to be translated into a series of elementary steps representing individual mechanisms. The modeler here is fundamental in the definition, what are the magnitudes considered as variables and which are not; This is a critical distinction that largely determines the output of the model. The development of the modeling approach currently has one of its major challenges, because it requires the different experts to share a common language. There is a need, next to the modeler, to familiarize yourself with the features and nuances of the system under scrutiny and speak in easy-to-understand terms by the part that is not of the model. On the other hand, the expert must adopt an integrative way of thinking and being able to explain his knowledge and express it in the most precise terms. Most of the time, it is necessary to repeat the stage of discussion and analysis several times, before the proposed model becomes able to respond successfully to all the objections that could be raised by the experts who come in contact with the model. Once you have reached an acceptable version you will be able to consider the next stage: the mathematical formalization. At this phase of the model building process it could happen that the modeler may be tempted by the challenge of building a wholly comprehensive model system, that is, one that takes into account, if not all, most of the characteristics of the real system. Besides the misunderstanding of the modeling process that this shows, this attitude has additional costs, because if two models serve to give the desired answers, the simpler one is better. A modeler intending to include all variables and parameters described would also be faced with the task of analyzing the influence of all the parameters on all the variables. This in turn would require an additional, usually non-negligible effort for its interpretation, making the model more difficult to understand. In modeling, more and harder is not necessarily better. In fact it sometimes happens that the largest and most complicated model may be the poorest in attaining its objectives or expressing necessary or meaningful details of the reality. A nice illustration of this point is the very simple model of the signaling pathway of NF-ÃºÂÃ²Â, in which with only three elements it is reproduced the main dynamical behavior of the original system (Krishna et al., 2006). In other words, we should try to make the complex as uncomplicated as possible. Despite this, the discussion of its results can enrich the conceptual model building when considering the traits and characteristics that were not initially included. Related with this is the fact that the developments of the conceptual model force the analysis and the systematic review of available knowledge about system and its behavior. as a result of this exercise of verbalization of knowledge -often unconscious- that experts have on the system, a new light is shed on the phenomenon, which often contributes to a better understanding of the system. It may happen that some information gaps on interactions u relevant parties that have so far been unnoticed become evident. this usually suggests new exploration pathways and ultimately contributes to a better understanding of the observed reality. In addition, discussions on the variables u the processes involved help to change previous assumptions u facilitates a new vision and understanding of some facts that previously remained unexplained. as an example, cheong et al. (2008) review the contributions of mathematical modeling on understanding the NF-κβ pathway. It is also very common to be aware of contradictions in understanding biological mechanisms. most of the knowledge u information on a subject can go through several undisputed authors, but when all this is mathematically formalized, problems arise to join all in a single framework. mathematical thought forces to reconsider every piece of knowledge. Finally, there is a modeling principle that should be commented here: "If the hypotheses of the model are erroneous, the conclusions raised from it will also be wrong." This principle should be taken into account during the entire process of modeling, particularly in the following mathematical formalization, because the resulting model must be faithful to the proposed hypothesis. ii. the mathematical translation of formalization the first question to be addressed in this new phase is on which mathematical formalism is best suited to represent the system (translation; see figure 1). there are many formal approaches to o odnes ,setnedneped res medopââ siev¡Ãirav .sortem¢Ãrap so e ).cte ,soriegasnem sANR ,sanÃetorp ,sotil³Ãbatem :adagitsevni eder ad socimÃuqoib sotsopmoc ed seµÃ§Ãartnecnoc(ââ siev¡Ãirav sa ertne sa§Ãnerefid sa oralc raxied someved ,oledom oN .)6002( effaY e senaJ me sadartsom o£Ãs sodad a adatneiro megaledom ed snumoc sacinc©Ãt sartuO .sciteniK )3191( netneM e sileahciM rop odad ©Ã nevirD-ledoM ed ociss¡Ãlc olpmexe mU .)oledom rop sadanoica( sacir³Ãet seµÃ§Ãaredisnoc ed seµÃ§Ãauqe sa odnavired uo etnemaciremun O etnemacitilana )avruc ad etsuja( socitsÃtatse sodot©Ãm ed osu od s©Ãvarta ,)sodad a adatneiro( etnemacaripme atief res edop o£Ã§Ãavired assE .siev¡Ãirav sa ertne laer acit¡Ãmetam o£Ã§Ãaler a odnecelebatse sadavired o£Ãtne o£Ãs seµÃ§Ãauqe sA .ametsis odââ siev¡Ãirav sartuo sa moc lanoicnuf o£Ã§Ãaler aus ed o£Ãsserpxe a eââ siev¡Ãirav siapicnirp sad o£Ã§Ãinifed a evlovne etnemlareg acit¡Ãmetam o£Ã§Ãalumrof ad lareg megadroba A .ocit¡Ãmetam atsiv ed otnop mu ed sodil¡Ãv res meved m©Ãbmat sam - socisÃf sossecorp ed somret me oditnes rezaf meved seµÃ§Ãacifilpmis sassE .sadizudortni res meved euq seµÃ§Ãacifilpmis s Ã odived o£Ã§Ãamixorpa ed ossecorp mu ©Ã oledom mu revlovnesed ed aferat A .amelborp od azerutan Ã acifÃcepse megaledom ed acinc©Ãt a ratpada ©Ã laedi edutita a saM .sodavorpmoc etnemaiverp e sodicehnoc siam sodot©Ãm so etnemlaicnereferp rasu larutan Ã .socitsÃnimreted o£Ãs socig³Ãloib samelborp so sodot men otaf ed odnauq ,acinc©Ãt assed atsiv ed otnop od samelborp so sodot radroba a rednet edop siaicnerefid seµÃ§Ãauqe odnasu megaledom me aicnªÃirepxe moc epiuqe amu ,olpmexe roP .ereferp uo animod euq megaledom ed sacinc©Ãt salep odazivarcse abaca asiuqsep ed opurg mu euq ecetnoca sezev satiuM .oledom od azerutan ad otium edneped ahlocse A .socinºÃ seµÃ§Ãatimil e setrof sotnop iussop seled mu adaC .)5102 ,lassaW e ywaalaklE rev ,o£Ãsiver amu arap( .cte setnega me adaesab megaledom ,socits¡Ãcotse sametsis ,sanaiseyab seµÃ§Ãauqe ,seµÃ§Ãauqe seµÃ§Ãauqe ed otnujnoc O .)1 arugiF a ajev( eled acit¡Ãmetam o£Ãsserpxe an lanoicida osrucer mu meussop ametsis od o£Ãsneerpmoc a e o£Ã§Ãaterpretni A .sasicerp sonem siautiecnoc seµÃ§Ãalumrof sa bos sodicehnocer o£Ãn marecenamrep euq sacitsÃretcarac e sossecorp malever ,sadanimaxe o£Ãn sezev s Ã ,siaicini seµÃ§Ãisopus sad seµÃ§Ãacilpxe sa euq ©Ã o£Ã§Ãazilamrof ed ossecorp od lev¡Ãduas aicnªÃ¼Ãqesnoc amu ,ossid m©ÃlA .oledom od airohlem a arap iubirtnoc euq o ,odibecrepsed rassap airedop ,amrof artuo ed ,euq ametsis o erbos sehlated o£Ã§Ãaredisnoc me ravel eved asiuqsep ed epiuqe a ,esaf atseN .selpmis somret me ametsis o revercsed a rodagitsevni o a§Ãrof lautiecnoc oledom od acit¡Ãmetam o£Ã§Ãalumrof amu ed otnemivlovnesed ed ossecorp O .oledom oirp³Ãrp osson oa saossep sartuo ed sovitejbo e seµÃ§Ãavitom sa riubirta oa odadiuc ret erpmes osicerp ©Ã ,otnatroP .serodairc sues ed sovitejbo e seµÃ§Ãavitom sad m©Ãbmat sam ,o£Ã§Ãurtsnoc aus arap sadasu sacinc©Ãt sad e atneserper ele euq ametsis od edneped sanepa o£Ãn oledom mu euq raredisnoc oir¡Ãssecen ©Ã m©ÃbmaT .aruturtse e etneibma ed sacifÃcepse seµÃ§Ãidnoc saus me odadutse res eved ametsis ovon adaC .aletuac moc adasu res eved ,arodatnet arobme ,aig©Ãtartse assE .ametsis ortuo revercsed arap odasu ©Ã etnetsixe oledom mu euq ecetnoca sezev satiuM .siatnemirepxe seµÃ§Ãavresbo ed ritrap a soditbo soxulf so omoc meb ,ossecorp od sotnemele so erbos sievÃnopsid seµÃ§Ãamrofni sartuo e socit©Ãnic sodad margetni soledom so ,etnemlareG .)8002 ,7002 ,.la te areV( sacim¢Ãnid seµÃ§Ãabrutrep ed siatnemirepxe sodad uo )0002 ,tioV( ametsis od siasabââ siev¡Ãtse sodatse so erbos seµÃ§Ãamrofni omoc ,roiretna ocig³Ãloib otnemicehnoc odnasu sodanimreted o£Ãs sortem¢Ãrap so arap socifÃcepse socir©Ãmun serolav sO .ametsis on sanretxe e sanretni seµÃ§Ãirtser menifed sortem¢Ãrap sO .).cte ,Hp ,zul( otnemirepxe o etnarud sodalortnoc res medop euq so odnes ,etnednepedni e ;)sodatse ed odamahc m©Ãbmat( ametsis od odatse o moc odroca ed opmet o moc mairav euq ¡Ãres ¡Ãres etnemlevavorp ocit¡Ãmetam oledom with the multitude of mathematical techniques and tools that allow the description and analysis of complex interrelated processes that occur in the real system; these techniques can help to elucidate the structure, properties and dynamic behavior of the system. These analyses may reveal details about the behavior of a model, such as the occurrence of oscillations or other complex behaviors that are often the motivating force to study these systems. Estimation of parameters and quality assessment Since the conceptual model has been translated into its mathematical form, the model must be supplied with the values of its parameters. The estimation of the parameter or calibration of the model is a recurring issue in the process of building the model; it is the discovery of numerical values that characterize the mathematical representation of a given system from experimental data (Park et al., 1997). A key feature of these experimental measures is that they must come from variables representing their main characteristics both at a certain time, and throughout their evolution over time (Polisety and Voit, 2006; van Riel, 2006; Ashyraliyev et al., 2008; Banga, 2008). In addition, the quality of the model should be tested through some numerical quality assessments. The model's quality assessment includes the evaluation of aspects such as the stability of stationary states, prerequisite for any model describing real biological systems; and the robustness of the model, a test to evaluate whether the model is able to tolerate small structural changes (Savageau, 1971; Hsiung et al., 2008) and the dynamic characteristics that characterize the transitional responses to temporary disturbances or permanent changes (Wt 2008). These analyses often point to problems of consistency and reliability of mathematical representation (Okamoto and1984, 1986; Ni and Savageau, 1996a,b); this constitutes a new of model refinement (Figure 1, light blue cycle). These changes result in improvements of the initial conceptual model. The conceptual model so improved will in turn suggest further experimentation leading to a new refined version that is enriched from the formalization phase. At all instances it should be borne in mind that both the parameters and the structure of real systems change over time. Therefore, a given model, which can be satisfactory at one time or certain conditions, may lose its effectiveness at another time or in other conditions. But the equations by themselves do not contribute much to the understanding of the system. It is necessary to solve the equations for some representative values of the parameters. Accordingly, the model is submitted to the simulation and validation processes. Simulation and Prediction The mathematical model should be programmed in the computer. The computer program is the translation of the mathematical model to another language useful for computing purposes. There are many computer languages and platforms to deal with this task; advances in computer numerical analysis have made the solution of complicated systems fast and accurate. It is at this point where computation becomes critical, since the equations describing biological processes nearly always involve control and regulatory mechanisms that have non-linear components. In contrast with linear differential equations that often can be solved analytically, non-linearities make it generally impossible. But through the use of numerical methods implemented on computers we can obtain good estimates and model predicted data. Model Validation Validation stands here as the correspondence between the real system and the mathematical model. A model can be considered good and useful only if its predictions in a given scenario agree with the experimental observations made on the actual system setting. As it is shown in the Figure sanepa ed o£Ã§Ãudortni a uo ,lautiecnoc oledom od eset³Ãpih ad a§Ãnadum e o£Ãsiver a rigixe arap etneicifus o sednarg res medop saicn¢Ãpercsid sA .lautiecnoc uo/e ocit¡Ãmetam oledom od o£Ã§Ãurtsnoc an sodasu sotsopusserp son sorre macidni sadavresbo saicn¢Ãpercsid sa ,osac reuqlauq mE .siamron seµÃ§Ãidnoc me ¡Ãratse ele o£Ãtne ,samertxe seµÃ§Ãidnoc me meb ametsis o atneserper oledom mu es ,euq ©Ã ossid s¡Ãrt rop acig³Ãl A .sahlaf saus ed arucorp Ã etnemadarebiled ,samertxe seµÃ§Ãidnoc a oledom o ratiejus evlovne sosac snugla me adasu res edop euq acinc©Ãt amu ,etnemlaniF .)2002 ,.la te ergeS( laer otnematropmoc ues oa o£Ã§Ãaler me ednopser ametsis o omoc ravresbo e sievÃsualp etnemacigoloib serolav ed amag ad ortned soledom snugla ed sortem¢Ãrap so rairav ©Ã litºÃ acinc©Ãt amu ,sosac snugla mE .)3102 ,serroT e sotnaS( oledom osson od seµÃsiverp sa moc o£Ã§Ãarapmoc a arap sodad sesse rasu arap sam ,oledom oirp³Ãrp osson od otnemivlovnesed o arap o£Ãn ,seµÃ§Ãidnoc samugla me sievÃnopsid sodad so sodot rasu ©Ã arienam artuO .setnahlemes sametsis me asiuqsep ed sopurg setnerefid rop soditbo sodad moc ;siaicini seµÃ§Ãidnoc sartuo ,samugla ed siev¡Ãirav sad o£Ã§Ãulove a rarapmoc ©Ã mU .o£Ã§Ãadilav ed ossecorp o ratucexe ed sarienam sair¡Ãv metsixE .sadavresbo saicn¢Ãpercsid sa raziminim arap o£Ã§Ãacifidom amugla rigixe edop oledom o ,odatluser omoC .etnerefid o£Ã§Ãidnoc amu ed siatnemirepxe sodad sovon moc ,odnuges mu sioped e ,edadilauq ed o£Ã§Ãailava e o£Ã§Ãarbilac ed olcic oriemirp mu oir¡Ãssecen ©Ã ,o£Ã§Ãadilav ed snif arap ,1 arugiF an odartsom ©Ã omoC .siatnemirepxe seµÃ§Ãidnoc sadanimreted me ,laer ametsis od e oledom od sair³Ãtejart e adÃas ed serolav sod savitarapmoc seµÃ§Ãavresbo me es-raesab edop ³Ãs o£Ã§Ãadilav ed ossecorp O .)seµÃ§Ãautis ed ovitacifingis oremºÃn mu me erroco ossi odnauq e( setnahlemes sodatluser zudorp siaer so moc satsiverp sadÃas sad o£Ã§Ãarapmoc a odnauq etnemos oinÃturcse o bos ametsis od levÃsualp o£Ã§Ãatneserper amu omoc oledom o ratieca somedop modifications to the parameters of the mathematical version. It should be remembered that the quality of a model depends directly on the quality of the information on which it is based. This statement is only the translation into the context of modeling the classical motto: "garbage in, garbage out". A mathematical model logically processes the information with which it was built; it cannot recognize or correct errors in the definitions or in the input information. The model forecasts are the result of the assumptions used, hence the extreme importance of taking care of the conceptualization phase and the quality of the initial information. Often the most important results of this phase are negative: a well-designed model would serve to rule out a particular mechanism as an explanation for experimental observations. After sufficient validation, we will reach a mathematical version of the model which can be used to perform experiments in the same way as in the real system. A model is considered valid in this regard when decisions made using the mathematical model are "similar" to those who would have been physically experimenting with the real system. This model version and its computer counterpart allow test conditions that can be difficult to achieve in the laboratory, or that have not yet been examined in real experiments. Each numerical solution of the model provides a simulation of a real or potential experience in the Real System. As an example of mathematical simulations that were useful to understand the dynamics of the cell membrane, an elusive biological process under laboratory experiments sees Marrink and Tieleman (2013). At this stage, from a first version of the mathematical model we have come to an improved version, validated, through a new virtuous cycle (clear blue arrows) that sums up to the first (clear pink arrows). RepeatedHcaorppa gnisimorp ab ot ot ot ot ot ot ot twos neeb evah taht ,hcraeser snoitarepo dna gninim atdad htid noinibmoc of Gnilodom Lacitamehtam Gnisu Derewsna Yllonoitar snoitseuq epyteuq snoitseuq snoitseuq snoitseuq s mllanoiteuq snoitseuq .) sesoprup lacidemoib ro lacigolonhcet htiw sessecorpoib fo tnemevorpmi eht ni stsitneics-oib troppus ot redro ni hcraeser snoitarepo htiw denibmoc eb nac gniledom lacitamehtam ,niev siht nI .noitazimitpo sti dna metsys eht fo tnemeganam demrofni swolla ti :stifeneb lanoitidda neht sah ledom a hcus fo ytilibaliava ehT .depoleved saw ti hcihw rof esoprup eht rof luftiurf dna lufesu si ti fi evitcejbo sti sllifluf ledom A noitazimitpO dna tnemeganaM .III .esahp noitazilautpecnoc eht ni denifed stpecnoc dna sesehtopyh eht fo ecneuqesnoc tcerid a era stluser sÃÂ¢ledom eht Taht nevig ,deyolpme seuqinhcet lacitamehtam eht suorogir in the dilav in the era snosulcnocnoc lacigol eht ,lufsseccus saw ssecorp noitazaloutpecnoc eht ,taht raelc em dluohs tluohs. niop siht tA .metsys laer eht dna ledom eht neewteb snoitaicossa elbisualp eveihca ot eb dluohs mia etamitlu ehT .ledom eht fo stluser dna secneuqesnoc eht fo ytidilav eht ezicitirc dna etabed ot ytinutroppo na si ereht ,egats siht tA .gnidnatsrednu dna noitaterpretni sti ni ecnavda Nac ew metsys laer eht fo noisrev lacitamehtam dnuos a dehcaer evah ew ecno noiterpretni dna tnemenefer ledom .tniop siht because ssecorp eht pots ot ot A ot ot netfo netfo etfo netfo etnilav eht .tniop eht .tniop ta ta POTs ,REVEWOH ,)dohtem cifitneics eht fo deedni ( ledom a gnipoleved fo ssecorp eht eptesse ,spool kbred Eht fo tset desaibnu na sdivorp taht ledlem lautpecnoc ht dna lacitamehtam eht htob our stnemevorpmi rehtruf is Tluser Nac Pool Hcraeser hguorht fo kcal eht fo esuaceb noitazilareneg dna tnempoleved rof snoitatimil ereves sah osla sessecorpoib fo gniledom lacitamehtaM .scitamrofnioib dna sciteneg ,yrtsimehc sa cissalc eht ot noitidda ni ,senilpicsid wen rehto gnoma ,gnitupmoc cifitneics dna ,scimanydomreht ,scitamehtam ni dnuorgkcab dilos dna daorb a edulcni taht stnemele htiw setaudarg ecneicsoib wen eht fo esab gniniart eht gnidnapxe dna gnipahs seriuqer hcaorppa evitargetni eht fo noitaroprocni eht sevlovni taht tfihs mgidarap ehT .noitulove derised siht deriapmi sah secneicsoib ni ksat gniledom eht yb deriuqer gniniart eht fo erutan lacinemuce eht taht tcaf fo rettam a si The ,tsrif .etercca ot dnert siht rof tsum tsum taht snoitidnoc owt ereht ,ylterruc .sleddom dliub ot ot ot deraperp eb tsitneics-oib snoib ni ,REVEWOH .)4102 ,.La te ressiv ;2102 ,.La te aznal ;1102 ,.La te renbâ1â1â1⁄4ative( secneicsomeb ni smelborp Tn hcaorppa gniledom eht Fo fo fossenlufesu dna fo ecnedive elpma nayerla ereht .stitneics )laicos neve dna( larutan ot ot ot sbhat yt yuqt sâyht sâsâ sa elbissop edam saw gniledom lacitamehtaM skrameR gnidulcnoC .ledom lautpecnoc devorpmi rehtruf a ot gnidael ,eno suoiverp eht ot sesopmirepus taht )sworra elprup( elcyc suoutriv evitareti rehtona hguorht ledom eht fo tnemenifer eht ot etubirtnoc sesylana eseht )evoba noitces tnemssessa ytilauq dna noitamitse retemarap eht Ees( sesht ni Lausu in ,dna ,dna .)noitces tnemsses ytilauq dna noitamitse retemarap eht Ees( me metsys laer a FO Noitattnesper Elbatius Nev ot, tilremrem stilauq stilauq stilauq yna sa ,Ledom Dezimitpo Eht .)0102 ,.La terev( hcraeser snoitarepo dna )7 wen fo noitisoporp eht tub ,noitarolpxe fo saera detcepsusnu ylsuoiverp fo gnidnif eht ylno ton setatilicaf tI .noitamrofni elbaliava eht fo noitaruc eht dna ,sevitcejbo sÃÂ¢ledom eht fo noitinifed eht seilpmi gniledoM .ecneirepxe yranilpicsidretni eht morf thgisni elbaulav morf detifeneb era seitrap lla ksat siht nI .srehto dna ,scitamehtam dna sciteneg ,yrtsimehcoib ,ygoloib ralullec sa hcus senilpicsid dehsilbatse gnoma ecafretni elitref eht :poleved stcejorp gniledom lacipyt eht fo tsom erehw aera eht si sihT .sledom detacilpmoc fo snoitacifilpmis dilav eht fo noitceles eht dna ,sdohtem laciremun reporp eht fo ecioh eht sa hcus sesylana rof deriuqer si snaicitamehtam decneirepxe htiw noitaroballoc eht ,revewoH .metsys eht fo roivaheb cimanyd dna seitreporp ,erutcurts eht fo egdelwonk eht nepeed ot pleh nac smetsys xelpmoc eht fo sisylana dna noitpircsed eht wolla taht sloot Lacitamehtam eht Fo eht hguorht metsys eht fo gnidnatsrednu .)3102 ,serrot ;2102 ,Tiov( pasiht llif ot elbaliava ydaerla si lairetam emos dna drager siht ni ssenerawa gnisaercni na si ereht ,yletanutroF .seuqinhcet gniledom ni osla tub )snoitauqe laitnereffid yranidro sa hcus stpecnoc lacitamehtam rehto ni osla dna scitsitats ni( scitamehtam ni ylno ton tneulf eb dluohs yrutnec IXX eht fo stitneics lacigoloib eht taht tcaf eht si elbadiovanu smees tahw tuB .)9002 ,pmeK dna tioV( ot desopxe eb dluohs stneduts secneicsoib eht tnetxe tahw ot dna stnetnoc tahw ot sa noissucsid emos si erehT .stneduts eht fo gnikniht lacitamehtam depolevedrednu yllamron eht htiw laed dluoc hcihw ,stnetnoc lacitamehtam detpada 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The 1102 ,Gineok ;6002 ,Sttaw dna Stna Stna Stna sttaw( SEPAUDARGTSOP ECNEICSOIB YNAM ni Devresbo Httam od e setnaveler seµÃ§Ãamrofni sad oÃ§Ãaterpretni e esil¡Ãna a e ohlabart od ngised e oÃ§Ãpecnoc a arap uiubirtnoc DN rotua ed seµÃ§ÃiubirtnoC .sacifÃcepse saferat razilaer arap sodidneterp socig³Ãloib sametsis arap sotejorp rareg arap sacit¡Ãrp sacinc©Ãt a ravel medop euq )3102 ,neerG e reuahneklоW ;1102 ,.la te odavlaS ;6002 ,nolA ;6791 ,uaegavaS( ocig³Ãloib ngised on levÃssop ©Ã euq o erbos seµÃ§Ãamrofni retbo arap sodazilaer odnes oÃtse so§Ãrofse sO .solpmexe sessed siareg soipÃcnirp ed oÃ§Ãavired Ã somirefer son s³ÃN .adiceuqse res eved oÃn euq etneuqesbus e avitudni aferat amu etsixe ,azerutan an sievÃnopsid solpmexe odnavresbo ,soviv somsinagro ed ohnesed od odutse o ajes lauta acig³Ãloib asiuqsep an mumoc siam megadroba a arobme ,euq raton es- eved ,etnemlaniF .ofos³Ãlif od lareg siam avitcepsrep a e oriehnegne mu ed air¡Ãtilitu e acit¡Ãmgarp siam oÃsiv a ertne ohnimac oiem a ¡Ãtse rodaledom mob mu ed laedi oÃ§Ãisop A .ovitejbo o erpmes ©Ã adavresbo edadilaer ad oÃsneerpmoc amu ra§Ãnacla sam ,sodad soa odatsuja ©Ã oledom o euq me aleuqa aires aterroc oÃ§Ãisop A .edadilaer ad oÃsneerpmoc rohlem amu a oÃ§Ãneta ratserp mes sam ,siaer sodad soa oledom o ratsuja ©Ã ovitejbo o meuq arap ,acit¡Ãmgarp oÃsiv amu moc eleuqa ©Ã ,ossi a otsopO .edadilaer a atneserper aditbo acit¡Ãmetam aruturtse a ,sele araP .adazirolav ©Ã oÃn avitudni oÃsnemid a lauq on latnem ossecorp mu omoc oledom od oÃ§Ãurtsnoc a maredisnoc euq satsilaedi so metnem ,odal mu eD .samertxe seµÃ§Ãisop saud ertne meb ¡Ãtse serodaledom sod airoiam A .acit¡Ãmetam esil¡Ãna e oÃ§Ãatupmoc ad aicnªÃic ,lanoicarepo asiuqsep omoc ,setnatsid )etnemetnerapa( sartuo moc m©Ãbmat sam ,)acit©Ãneg e aigoloiborcim ,ralulec aigoloib ,acimÃuqoib ,olpmexe rop( sacig³Ãloib sedadilaicepse ertne sanepa oÃn aditnes ©Ã arodacifinu oÃsnet assE ;sacifÃtneic sanilpicsid ed oÃsuf a etnemlarutan atilicaf m©Ãbmat otxetnoc essen megaledom ed acit¡Ãmetsis acit¡Ãrp A .atsinoicuder megadroba ad setnedive mare oÃn euq by sledom lacitamehtam .)0102( .c ,zevahc-oltsac dna ,.f ,Reuarb Ralohcs Elgoog .32ââ€TM ,fried up Eht Fo sgnidecorp â€â€â,?Ygoloib lacteroeht ETanimulli Sleddom Citupmoc citsilarerern nacâœâ€Toc .)9 .j/1111.01 :iod .209â"â€â¢688 ,672 .J Sbef .Ledom Lacimehcoib ROF Noitamitse Retemarap :ygoloib Smetsys kcafnaN-gnokemoF ,.M ,veyilaryhsA ralohcS elgooG .rehsilbuP llaH dna nampahC :nodnoL .stiucriC lacigoloiB fo selpicnirP ngiseD :ygoloiB smetsyS ot noitcudortnI nA .)6002( .U ,nolA ralohcS elgooG | txeT lluF feRssorC | tcartsbA deMbuP 3869210.enop. lanruoj/1731.01 :iod .3869210E:01 ENO Solp .Suac ytisebo fo margaid smetsys desab Ytummoc .)5 O ,Ellyrb ,.S ,Rednella secnerefer .noitarballoc el baulav reh rof ideleF anilataC .rD dna lebeuG leinaD .rD htiw snoissucsid egdelwonkca srohtua ehT tnemgdelwonkcA .ylevitcejbo detcudnoc saw ssecorp weiver eht snoitaroballoc suoiverp rieht etipsed taht eralced sevlA iuR rotidE gnildnah dna oynirpaliV retsE reweiver ehT .tseretni fo tcilfnoc laitnetop a sa deurtsnoc eb dluoc Taht Spihsnoer laicnif ro laicremoc y fo ecnesba eht ni detcudnoc sawnoc sawnoc sawnoc sawnoc hcraeser eht taht eralced srohtua eht tnemetattni Fo Tcilfnoc .niarbmi-73613-2102tc-2 tcejorP ,OCENIM morf stnarg hcraeser yb dednuf saw krow sihT gnidnuF .dehsilbup eb ot noisrev eht fo lavorppa lanif eht evag oslA .tnetnoc sÃÂ¢ti fo noisiver dna gnitfard eht dna noitamrofni tnaveler eht fo noitaterpretni dna sisylana eht dna krow eht FO ngised dna noitpecnoc ot detubirtnoc Sg .Dehssilbup Eb ot Noisrev Eht Fo Lavorppa lanif eht evag osla .tnetnoc sâ€â€â€ti Fo Noisiver dna Biology and Epidemiology. 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