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Computational Systems Biology for Aging Research

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Abstract

Computational modelling is a key component of systems biology and integrates with the other techniques discussed thus far in this book by utilizing a myriad of data that are being generated to quantitatively represent and simulate biological systems. This chapter will describe what computational modelling involves; the rationale for using it, and the appropriateness of modelling for investigating the aging process. How a model is assembled and the different theoretical frameworks that can be used to build a model are also discussed. In addition, the chapter will describe several models which demonstrate the effectiveness of each computational approach for investigating the constituents of a healthy aging trajectory. Specifically, a number of models will be showcased which focus on the complex age-related disorders associated with unhealthy aging. To conclude, we discuss the future applications of computational systems modelling to aging research.

Aging has intrigued and troubled scholars since the beginning of civilization. It is a process that can be described generally as the changes that take place during the life span of an organism which progressively renders them more likely to die. The alterations that bring about a gradual increase in the probability of mortality involve all aspects of biology, from molecular mechanisms to whole-body physiological systems. Moreover, there is little doubt that aging is modulated extrinsically by diet, while intrinsically the velocity of aging also appears to be shaped by a wide variety of genetic mutations. For instance, mutations to daf-2/daf-16 regulate life span in the nematode [1], while the FOXO3A genotype has been strongly linked with variations in human longevity [2]. Paradoxically, genetic homogeneity does

not mean the velocity of aging will be the same, as genetically identical species can display a variety of aging rates [3]. Furthermore, evolution has given rise to significant life span variations between different species [4]. Aging is also seen as central to the understanding of many disease states; for example, in certain tissues the accumulation of senescent cells can lead to cancer via a pro-inflammatory response [5], while neurodegeneration underpins the progression of Alzheimer's (AD) and Parkinson's disease [6]. Moreover, free radical damage has been implicated in a variety of disease pathologies from cardiovascular disease (CVD) to dementia. Historically, biologists have investigated the complexities of aging using conventional wet laboratory techniques; however, it is increasingly recognized that to fully appreciate the uniqueness of aging, systems biology approaches are a necessity [7]. A fundamental aspect of systems biology is computational systems modelling, a procedure which involves the development of in silico models. Such models are ideal for describing the innate complexity and dynamics of aging. However, it is often misunderstood as to what exactly computational systems modelling is. It is not statistical data analysis, the three-dimensional visualization of proteins or database mining; instead, it involves using a computer to quantitatively represent the components of a biological system of interest. How the components interact based on current biological understanding is described with mathematical equations. The computer then simulates the interactions between the components to give an overall graphical account of the dynamics of the system [8]. Thus, computational systems modelling can be easily integrated with other disciplines under the systems biology umbrella, as quantitative data from diverse fields including genomics, metabolomics and proteomics can be utilized to inform model construction and refinement. Moreover, model predictions can be used to direct the future design of wet laboratory experiments and also give insights into how a biological system will behave under a wide-variety of different conditions. For instance, the proposed effects of the aging process can be incorporated into a model by including something as straightforward as the age-associated decline in the activity of the key enzymes of the cellular pathway of interest. Despite the clear advantages outlined above, the utility of modelling to aging research can often be overlooked, or traditional gerontologists can be sceptical about the validity of the model or the modelling process generally. Thus, it is important to extend further the rationale for using computational systems modelling and why it is central to improving our understanding of the aging process.

Rationale for Using Systems Modelling for Aging Research

As outlined, computational models are capable of the quantitative representation and analysis of biological systems, something that is not always possible to achieve in a wet laboratory for a number of reasons. Firstly, biological systems are both in-

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herently detailed and inherently complex. This level of detail and complexity gives rise to a diverse web of overlapping metabolic networks which are comprised of multiple connections between each node in the network. Many of the nodes interact in a non-linear fashion and often communicate with each other via sophisticated feedback or feed-forward loops. This places a significant cognitive burden on the human brain to retain this level of complexity and detail. For instance, if the activity of NAD+ dependent deacetylases, commonly referred to as sirtuins are explored, such complexity becomes apparent as the seven mammalian sirtuins perform numerous interrelating actions and modulate a number of pathways connected to age-related disease [9]. Likewise, the mammalian target of rapamycin (mTOR) pathway is equally complex. This system is known to regulate life span in model organisms, and recently has been suggested as a central intracellular regulator, mechanistically connecting aging, oxidative stress and cardiovascular health [10]. Thus, it is highly improbable that one can reason about such complex systems by human intuition alone and as such computational modelling offers a complimentary means of dealing with the complexity associated with aging. Another reason for using the systems approach is to identify and unravel molecular and biochemical hubs that are key regulators, whose robust dynamics ultimately impact the health of tissues and whole-organ systems. To this end, computational systems biology is beginning to accommodate the representation of biological systems in a multi-scale way [11, 12]. This type of representation contrasts with many conventional methodologies which focus on a small manageable component of a biological system. This is particularly significant for aging, as the most probable way to gain a deeper understanding of this intriguing phenomenon is to investigate the synergistic behaviour of cells, tissues and organ systems. The next section will explore further the advantages of computational systems biology compared to conventional approaches to studying aging.

Advantages over and Interactions with Conventional Techniques

There are many conventional approaches that can be used to study aging. These experimental methodologies have been valuable in aiding our understanding of the aging process and will have a role to play in future aging research; however, such methodologies have limitations. If for example longitudinal studies are examined, this approach certainly has value; however, it can be resource intensive, expensive and time consuming. Most significantly, this approach will not offer immediate benefits for an aging Western population which urgently requires remedies to diseases such as dementia, which almost half of the oldest old (those ≥85 years) in the USA and UK suffer from [13]. Cross-sectional studies, where individuals of varying ages from a population are assessed at the same time point are not as costly as longitudinal investigations. However, distinguishing cause and effect in cross-section-

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al studies from straightforward association is inherently difficult. As an example, recent evidence has indicated an association between the decline in global DNA methylation and age in humans. DNA methylation is an epigenetic mark that plays an important role in gene expression, gene imprinting and transposon silencing. Paradoxically, advancing age has been associated with the hypermethylation of certain genes, which can result in age-related disease [14]. If a cross-sectional study was conducted to examine DNA methylation status in a cohort of individuals, this phenomenon would more than likely be apparent. However, it would be challenging to disentangle its causes, as a wide variety of intrinsic and extrinsic factors are conjectured to modulate DNA methylation. These factors include a methyl-deficient diet, genetic polymorphisms within the folate pathway and age-related alterations to the activity of DNA methyl transferases, the family of enzymes responsible for transferring methyl groups to the DNA molecule [14]. It is possible that heterogeneous individual combinations of these factors could independently result in the methylation paradox and a cross-sectional study would not be able to unravel this. The significance of biological heterogeneity is further emphasized by the knowledge that clonal populations of cells display significant phenotypic variations. This phenomenon is suggested to arise from stochasticity or noise in gene expression [15]. Aging researchers need to be acutely aware of biological stochasticity and that simulations by computational systems models are capable of representing both inter-individual and inter-cellular stochasticity [16]. When studying aging, it is also important to take account of the ethical considerations, for instance dietary intervention studies are regularly employed to explore potential nutrients that could modulate the aging trajectory; however, there is a moral imperative to consider here. For example, rodents are routinely used to investigate dietary regimes in aging research; but it could be argued that it is unethical to overuse animals in studies of this nature. Significantly though, model organisms have helped to reveal that caloric restriction (CR) can extend life span [17]. However, this raises the issue of whether such findings can be translated to humans, as many difficulties surround these investigations, not least that extended timeframes are needed to decipher the optimal regime most beneficial to healthy aging. It is also important to be cautious when making inferences about the potential effects of CR in humans. We need only look to the disciplines of toxicology and pharmacology to recognize that the physiology of animals does not always translate well to humans. Thus, an in silico human representation of CR would be worth establishing prior to any trial of CR in humans, as modelling could help to reveal any potential dangers of this regime. This is not improbable as computational systems models are currently used to study the long-term effects of diet on the pathological signatures that characterize unhealthy aging [18]. Thus, computational systems modelling can overcome a variety of challenges by providing a framework for aging-centred questions that are unsuitable to test with conventional approaches.

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Computational Systems Modelling Approaches for Aging Research

Modelling approaches differ significantly from traditional in vivo or in vitro techniques used to study aging. Firstly, a model can be used as a cheap and rapid test bed for hypothesis exploration. For example, computational models have long been used for testing life history theories that attempt to frame aging within an evolutionary template [19]. Moreover, no matter what framework is used, constructing a model can improve or augment our understanding of the age-related process under examination. This is a result of having to consider the system of interest in an unambiguous and precise fashion using mathematics; and there are several mathematical frameworks which can be adopted to deal with the complexities of aging. The theoretical framework that is employed will depend on the nature of the system to be modelled. Importantly however the model needs to encapsulate the biological essence underpinning the aging process under consideration, and the framework that is employed should be directly informed by biological evidence and not by modeller bias for a particular approach.

Ordinary Differential Equations and Partial Differential Equations

This approach treats biological systems as reaction networks, which can be represented mathematically by ordinary differential equations (ODEs). ODEs are known as ordinary because they depend on one independent variable (time), and it uses the assumption that biological species exist in a well-mixed compartment, where concentrations can be viewed as continuous. It also assumes that large numbers of molecules are involved in reactions and that the average behaviour of the population of molecules is not influenced by variability [20]. ODEs can be coded on the computer and an algorithm solves them numerically to produce a deterministic output. They are the most common mathematical framework used in computational systems biology; however, they are unsuitable for modelling transport processes, diffusion, molecular spatial heterogeneity and stochasticity. The latter of these limitations is important for aging research as intracellular processes such as oxidative stress are often viewed as stochastic events. Recent examples of ODE models that have been employed in aging research include deterministic models used to represent apoptosis [21], immunosenescence in humans [22], and cardiac ventricular dimension alterations during aging in mice [23]. In contrast to ODEs, partial differential equations (PDEs) are multivariable functions with partial derivatives. Not as ubiquitous as ODE models, the main advantage of PDEs is the ability to handle both spatial and temporal dependencies. This is best demonstrated by a recent model of tumour growth, which included cell age, cell size, and the mutation of cell phenotypes [24]. Moreover, it also incorporated proliferating and quiescent tumour cells indexed by successively mutated cell phenotypes of increasingly proliferative aggressiveness.

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The model was able to structure tumour cells by both cell age and cell size. A disadvantage of PDE models is that they can be computationally intensive and thus slow [20].

Stochastic Reaction Networks and Probability-Based Models

Stochastic reaction models attempt to represent the discrete random collisions between individual molecules, which is vital when considering that random accumulation of cellular damage has long been implicated with intracellular aging. This type of reaction is suggested to take place if the molecules exist in small numbers or there are fluctuations in their behaviour, for instance variations in cellular free radical levels. Stochastic simulations treat molecule reactions as random events. Computationally, this approach involves an algorithm treating each reaction in the model as a probability/propensity function, e.g. reactions have different probabilities of occurring, which can be altered based on the reaction type. A stochastic algorithm is not concerned with average behaviour, rather the probabilistic formulation determines firstly when the next reaction occurs and secondly what reaction it will be [16]. Due to its historical connection with the free radical theory of aging, mitochondrial/oxidative stress models are commonplace. Recently, a stochastic systems model was used to simulate mitochondrial function and integrity during aging [24]. The model demonstrated that cycles of fusion/fission and cell degradation are required to maintain optimal levels of mitochondria, even during periods of stochastic damage [25]. Another recent model by Kowald and Kirkwood [26] examined the accumulation of mitochondrial DNA deletions with age in post-mitotic cells. Computer simulations were used to study how different mutation rates affect the extent of heteroplasmy. The model showed that random drift works for life spans of around 100 years, but for short-lived animals, the resulting degree of heteroplasmy was incompatible with experimental observations [26]. Another recent stochastic model focused on the age-related factors that contribute to neurodegeneration by investigating the potential role of glycogen synthase kinase 3 and p53 in AD [27]. The model was able to predict that high levels of DNA damage leads to increased activity of p53 [27]. A model based on the same field of study by Tang et al. [28] illustrates the complementary nature of computational modelling and wet laboratory experimentation. The authors used fluorescent reporter systems imaged in living cells and computer modelling to explore the relationships of polyQ, p38MAPK activation, generation of reactive oxygen species, proteasome inhibition and inclusion body formation. Several other probability/stochastic network models have attempted to replicate the dynamics of telomere erosion. For instance, a computational model was able to explore the idea that telomere uncapping is the main trigger for cellular senescence [29]. A more recent stochastic model made the assumption that cell division in each time interval is a random process whose probability decreases linearly with telomere shortening [30]. Computer simulations of this model were also able to pro-

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vide a qualitative account of the growth of cultured human mesenchymal stem cells [30]. Variability in biological systems can also be represented with a bayesian network (BN). BNs are a type of probabilistic network graph, where each node within the graph represents a variable. Nodes can be discrete or continuous and are connected to a probability density function, which is dependent on the values of the inputs to the nodes [31]. Recently, a special type of BN called a dynamic BN was applied to the Baltimore Longitudinal Study of Aging. The advantage of this approach over conventional BNs was its ability to model feedback loops. The model showed that interactions among regional volume change rates for a mild cognitive impairment group were different from that of a 'normal' aging cohort [32]. A limitation of BNs is that they are entirely probabilistic and do not represent biological systems mechanistically.

Petri Net Models, Boolean Networks and Agent-Based Models

Petri nets are a directed bipartite graph, with two types of nodes, called places and transitions, which are represented diagrammatically by circles and rectangles, respectively. Circles represent 'places' while rectangles represent 'transitions'. Places and transitions are connected via arrows/arcs. Each circle or place contains a number of tokens which is a kin to a discrete number of biochemical molecules, while the stoichiometry is indicated by the weight above the arrow/arc. Tokens can be both consumed and produced within the Petri net, while a Petri net functions by input-output firing at the 'transitions' within the network. The 'firing' of transitions is a kin to a biochemical reaction taking place. The firing of 'transitions' is controlled incrementally using time steps. There are many different variants of Petri net, including coloured, hybrid, continuous and stochastic, each having a slightly different mode of operation. Petri nets are ubiquitously employed to study genetic regulatory networks [33]. From an aging perspective, a recent Petri net model involved modelling the high osmolarity glycerol signalling pathway, an important regulator of several transcription factors that respond to oxidative stress [34]. The model focused on *Saccharomyces cerevisiae* and was able to successfully integrate key signalling, metabolic and regulatory processes in a systems orientated fashion. Boolean network models are also comprised of nodes that can either be in an 'on' or 'off' state. The dynamics of the model are acted out by a series of time steps, with the state of each Boolean variable being updated at each time step. Similar to Petri nets, Boolean models are regularly employed to examine gene regulatory networks. A recent example of a Boolean model relevant to aging research described the behaviour of the apoptosis network. The model provided insights into the interactions between pro- and anti-apoptotic factors [35]. Agent-based models have been increasingly used in aging research also [36]. This is a rule-based approach which is used to investigate biological systems using clusters of independent agents whose behaviour is underpinned by simple rules. These agents are capable of interacting with one another through space and time. Agent-based models have been applied

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to many areas of aging research, including signalling pathways, and immune responses. An agent-based model has recently been used to model the NF-κB (nuclear factor-κ light chain enhancer of activated B cells). The model incorporated individual molecules, receptors, genes and structural components such as actin filaments and cytoskeleton, while providing a detailed outline of this network [37].

Model Building

The steps in model building in aging research are presented in figure 1.

Step 1: Selecting a System to Model, and Step 2: Checking for Previous Models

Increasingly, modellers are becoming part of the infrastructure of modern wet laboratories, and in theory computational modelling should directly compliment the other systems biology techniques outlined in this book thus far. Therefore, the direction the computational model takes should be informed by the overall research focus of the wet laboratory and should also be integrated with other laboratory experiments [38]. Once an aging-focused system is identified, it is necessary to determine whether the model will simply describe the systems of interest or whether it will focus on predicting the behaviour of the system (a hypothesis-driven model). This decision should be determined by the goals and motivations of the research team. The team will then be required to decide on the components of the model. This is an abstract process, and it is not possible to include every biological species or reaction. As a rule of thumb, model boundary points should be informed by the idea or hypothesis that is under consideration. It is also important to perform a literature search to determine if the system of interest has been modelled previously. This step can be facilitated by the BioModels database, an archive of published peer-reviewed systems models (http://www.ebi.ac.uk/biomodels-main). Models archived in the BioModels database are coded in the model exchange framework, the Systems Biology Markup Language (SBML; http://sbml.org/Main_Page). If no suitable model exists, it will be necessary to develop a list of biological species and to determine how they interact with each other before visually displaying their interactions in a network diagram.

Step 3: Network Diagram Construction, and Step 4: Deciding on a Mathematical Framework

A network diagram is necessary to outline precisely how the biological species interact and to illustrate model boundary points. A variety of approaches can be used to do this,

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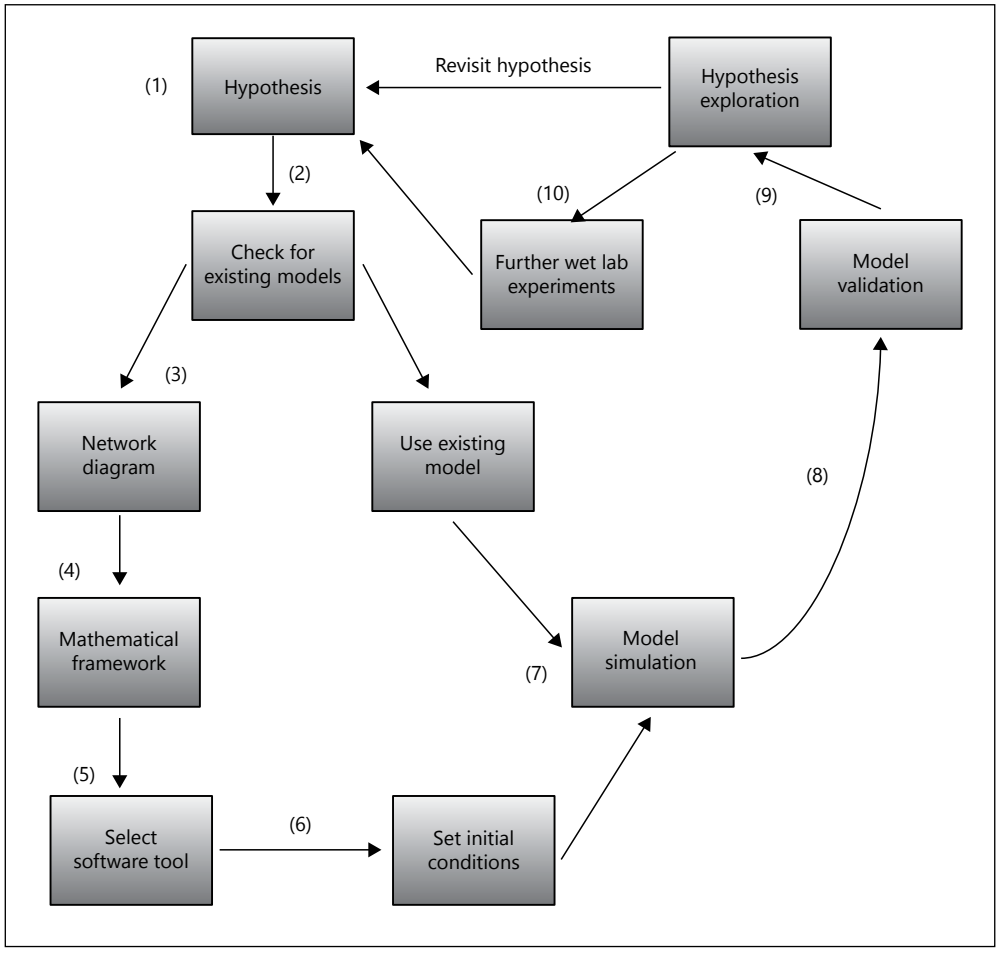

Fig. 1. The 10 steps involved in the modelling process; the process is cyclic with wet laboratory experimentation generating a hypothesis which in turn can be tested by constructing a model; the model in turn feeds further wet laboratory experimentation.

and recently an attempt has been made to standardize how network diagrams are represented using a framework called Systems Biology Graphical Notation [39] which could become the standard means of representing models diagrammatically in the future. To illustrate the network building process, an example of an elementary model of the mTOR signal cascade was developed (fig. 2). The purpose of including this diagram was firstly to illustrate the precise nature of network diagrams. Secondly, the diagram emphasizes that one must abstract when model building. For example, the mTOR signal cascade is a complex network, with >50 components; thus, it was necessary to be selective in order to identify key hubs in the pathway. The network diagram (hypothetical model) commences with the extrinsic stimulation of P13K by growth factors such as those from the

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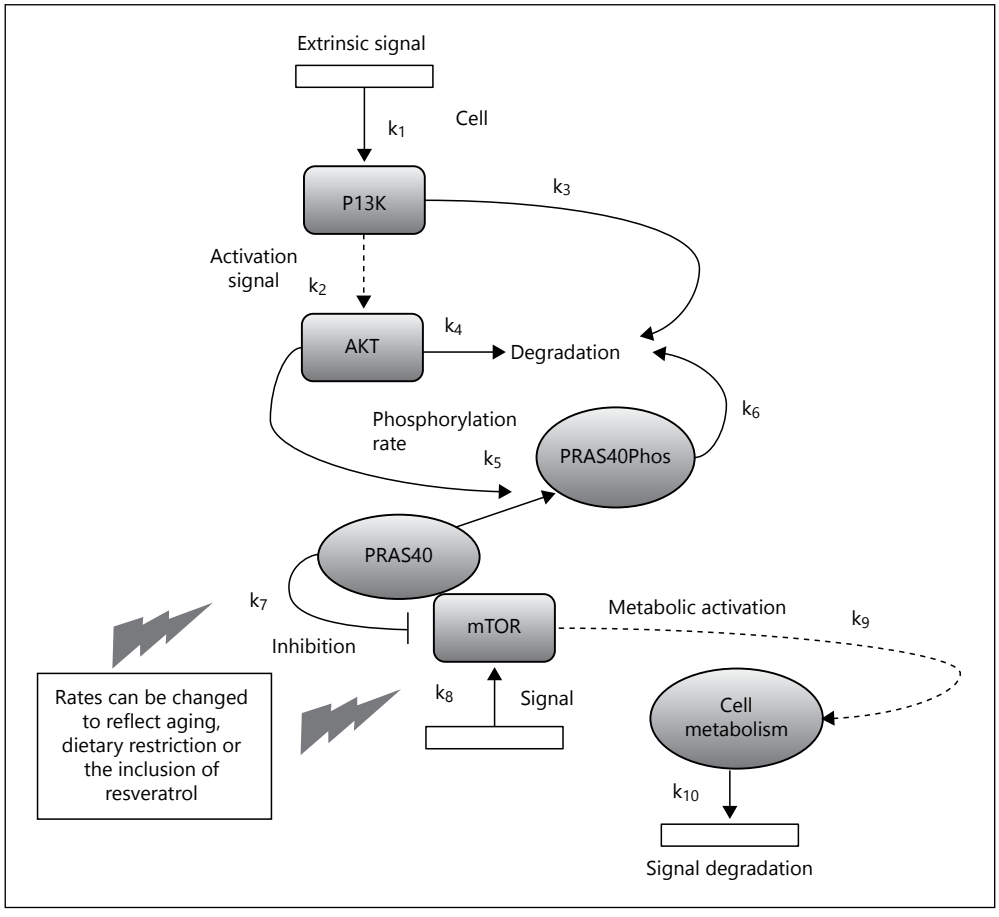

Fig. 2. Diagrammatic representation of mTOR signalling for illustrative purposes. Arrows represent stimulation or conversion reactions; while feedback inhibition is represented by T-shaped arrows. k_1–k_{10} represent kinetic reaction rate constants for each of the steps in the model. k_1 = Rate of activation of P13K; k_2 = rate of activation of AKT; k_3 = degradation rate of P13K; k_4 = degradation rate of AKT; k_5 = rate of PRAS40 phosphorylation; k_6 = rate of PRAS40 degradation; k_7 = inhibition of mTOR signal; k_8 = mTOR signal input; k_9 = metabolic activation; k_{10} = metabolic signal degradation; P13K = phosphoinositide 3-kinase; AKT = protein kinase B; PRAS40 = proline-rich AKT1 substrate 1; PRAS40Phos = phosphorylated PRAS40.

insulin-like growth factor family. This is significant from an aging perspective as CR inhibits the activation of this pathway. AKT is activated by P13K in a manner which depends on the rate at which P13K has been activated (reactions are indicated by arrows, with their kinetic reaction rates indicated by the symbols k_1–k_{10}). Both P13K and AKT have degradation rates. From an ageing perspective it would be worthwhile investigating how changes to these rates impact the system as a whole. Alterations to the levels of AKT have been implicated in the progression of age-related diseases such as cancer and

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type 2 diabetes; therefore, this is another aspect of the model that could be explored from an intrinsic aging perspective. Dietary regimes associated with longevity could also be investigated; for example, it would be straightforward to incorporate the effects of CR on this pathway or to include the proposed inhibitory effects of the phenolic compound resveratrol.

Step 5: Identify a Suitable Modelling Tool, and Step 6: Setting the Initial Conditions/ Parameters

There are many software tools available to build models of biological systems. Examples include commercial software packages such as Mathematica and MATLAB, while non-commercial tools include Copasi (http://www.copasi.org), CellDesigner (http://www.celldesigner.org/) and PyCml (https://chaste.cs.ox.ac.uk/cellml/). Until recently, it was necessary to learn how to programme competently to construct a computational model, which made the discipline inaccessible to many bioscience researchers. Recently, significant progress has been made, and many tools now come with a graphical user interface (GUI), for instance Copasi [40] and CellDesigner have intuitive GUIs. If the model is kinetic based, setting the initial conditions and parameters involves establishing the initial concentrations of the various biological species and giving each rate law a value. There are many online resources which can be utilized to help with this process. For example, BRENDA (http://www.brenda-enzymes.org/) and SABIO-RK (http://sabio.h-its.org/) archive the details of a wide variety of kinetic data including V_{max} and K_{cat} values which can be used to inform model parameterization.

Step 7: Model Simulation, and Step 8: Model Validation/Parameter Inference

The output from a simulation will depend on the type of mathematical framework that underpins the model. For example, a deterministic solution will always have the same output for a given set of initial conditions and parameters. A stochastic simulation will not produce the same output given a set of initial conditions and parameters. Output from the model can be compared with appropriate time course data to compare the dynamics of the system with its biological counterpart. The sensitivity of the model can also be explored by making adjustments to the model parameters/initial species concentrations. If the model does not compare well to the behaviour of the biological system, it will be necessary to 'fine tune' the parameters to ensure the behaviour of the model is consistent with the dynamics of the biological system. Certain software tools are capable of optimizing a parameter set (or sets) which is consistent with the experimental output. For example, the software tool Copasi has a number of inbuilt statistical techniques to facilitate parameter optimization.

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If the output of the model appears to be a realistic interpretation of the dynamical behaviour of the system, the model can be used as a predictive tool. If the model does not appear to be a realistic interpretation, one can refine the research question/model; thus, model building is a cyclic process that involves continual revalidation and re-evaluation of the model. If satisfied with the model it can be coded in an exchange format and several exist for computational models, including the Cell Markup Language (Cell-ML; http://www.cellml.org/) and SBML (http://sbml.org/Main_Page). Presently, SBML is the leading exchange format in systems biology and has been evolving since 2000 thanks to an international community of software developers and users.

Computational Systems Models of Aging – From Cell to Whole Body

As outlined, the aging process is inherently complex with a multitude of overlapping relationships that communicate over several different levels. This complexity is a direct result of the underlying multi-scale interconnectivity and interplay of a diverse range of molecular, biochemical and physiological processes. There is no doubt that aging and age-related diseases are a manifestation of the dysregulation and dysfunction of these systems. As a result of the multi-scale nature of biological systems, various different levels of abstraction have been used to create models of a diverse array of processes relating to aging. In the main, systems computational models are cellular in nature; however, recently several aging researchers have come to the conclusion that cellular models, although important are an insufficient means of representing the holistic nature of the aging process and its interaction with age-related pathologies. Consequently, several whole-body computational systems models have been developed. It is not possible to discuss every model; therefore, selections have been restricted to those that illustrate eloquently the diversity and utility of whole-body systems models which have been applied to aging research. For instance, a recent whole-body systems model of cholesterol metabolism was used to explore the interaction of this system with intrinsic aging. The model was able to show that changes to intestinal cholesterol absorption due to the aging process could result in a rise in low-density lipoprotein cholesterol (LDL-C), a key pathological signature of CVD. Moreover, the model also showed that decreasing the rate of hepatic clearance of LDL-C from half its initial value by age 65 years can result in the significant elevation of LDL-C [18]. Other age-related whole-body models have focused on brain aging and dementia. For example, a novel whole-body computational model integrated specific brain regions associated with AD together with the physiological regulation of the stress hormone cortisol. The rationale underpinning the model was to investigate the possible role elevated levels of cortisol have in damaging the hippocampus, the brain region which is the core pathological substrate for AD. The

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model was able to replicate the in vivo aging of the hippocampus. Moreover, both acute and chronic elevations in cortisol increased aging-associated hippocampal atrophy and concomitant loss in the activity of the hippocampus. The model was also used to investigate potential interventions such as physical activity which could be used to mitigate the effects of aging and cortisol damage to the hippocampus [41].

Conclusions

Computational systems modelling is a novel integrated approach that provides a powerful foundation for gaining an in-depth understanding of how human metabolism is perturbed by aging. This chapter has highlighted the rationale for using computational systems models. The steps involved in the model building process were also outlined, and a wide variety of models from cellular to whole body were discussed that emphasized the utility of modelling to aging research. It is highly probable that in future years computation systems modelling will be further embedded within systems biology. This is something that the aging research community will benefit from as coming years offer the possibility of models being connected together to create a holistic picture of the aging process from genes through to whole organ systems. Such models could focus on multi-scale responses to nutrients or physical activity over extended time frames. In order to achieve this goal, there is little doubt innovative collaborations are a necessity. As this chapter has highlighted, building computational models is a highly collaborative effort that requires considerable interaction between several disciplines. Thus, it is not a process that should occur in isolation as it needs to be firmly integrated within the systems biology paradigm. Working together mathematicians, computer scientists and experimental biologists will be able to provide valuable insights into how robust biological systems break down due to the aging process. Such insights will no doubt contribute to the development of strategies which help to prolong healthy life and delay age-related diseases such as CVD and dementia.

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Yashin AI, Jazwinski SM (eds): Aging and Health – A Systems Biology Perspective.
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