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Biexcitability and Bursting Mechanisms in Neural and Genetic Circuits

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Abstract: This paper compares mechanisms for generating repetitive spikes (bursts) in neural and transcriptional circuits. Neurons generate bursts followed by refractory periods controlled by ion channels in the membrane. In contrast, in gene transcription the bursts occur during a short time period followed by silent periods regulated by sis-regulatory elements. The role of excitability in producing different patterns of bursts is discussed by comparing the topology of a neural model with natural and synthetic transcriptional genetic circuits. In particular, a special bi-excitable architecture which embeds two excitable states are compared in these systems.

1. INTRODUCTION

Information coding and decision making is complicated in cellular machinery. Genes, proteins and metabolites are assembled into core biological networks to form decision-making circuits. These networks are remarkably flexible and evolve due to their high degree of modularity. Therefore, new circuits can arise by relatively simple manipulation leading to highly innovative regulatory behaviours.

A wide range of temporal gene expression patterns in response to triggering inputs has been identified (Yosef and Regev 2011). These responses include a single pulse, a train of pulses (burst), sustained state-transitioning patterns and oscillations. The architecture of these networks is tuned during evolution to perform responses with appropriate timescales. These timescales can range from rapid responses, i.e. minutes to hours, to slow responses, i.e. hours to days, during development (Lopez-Maury, Marguerat et al. 2008). The triggering inputs can be external or internal signals or intrinsic noise. The architectures of these networks are optimized to be highly selective to particular inputs and robust against undesirable perturbations.

Most genes show transcriptional bursts in their activity pattern which means they are active for a short period interspersed with inactive (silent) periods. Recent single-cell studies in mammalians have revealed that active and inactive periods are highly gene-specific. In other words, the inactive period is constrained by the presence of refractory mechanisms before a gene can be turned on again (Suter, Molina et al. 2011). Bursting has been recognised in a variety of systems from bacteria and yeast to mammalian cells and developing embryos (Eldar and Elowitz 2010).

In contrast, neural networks receive sensory information, analyse it, make decisions and execute movements. Most nerve cells generate a series of voltage pulses (bursts) with different shapes, each having a specific characteristic as a unit of neural data communication. These discrete groups or bursts of spikes are followed by a period of quiescence before the next burst occurs. Bursting plays a crucial role in neural communication (Izhikevich 2007).

Although the molecular components which produce this bursting in genetic and neural circuits are different, the architectures and topologies of these networks are comparable. In this paper the architecture of two systems which generate transcriptional and electrical bursting will be compared. This comparison will help us to understand why nature has chosen and conserved specific architecture during evolution to perform the same dynamical behaviour for both neural and genetic circuits. Also, such understanding helps us to choose appropriate design principles to construct new synthetic circuits in the new field of synthetic biology.

In this paper we are particularly interested in a circuit architecture with two stable states which are excitable. We call it biexcitable (bistable excitability) and we will show that two types of excitability coexist in this configuration. We will compare the architecture of a neural, genetic and synthetic circuit which can produce such behaviour. The rest of the paper is organised as follows. Section 2 discusses the stochastic state switching and proposes a bottom-up approach to generalise the characteristics of a small core network using the theory of nonlinear dynamical systems. Section 3 discusses the bursting mechanism and biexcitability in a neural model. Then the existence of similar behaviour in an analogous genetic circuit will be discussed in Section 4. In

Section 5, the topology of a synthetic circuit which has been designed to perform oscillation will be analysed to explore its capability to perform more complex behaviour such as synthetic pulse or burst generator. The last section of the paper is discussion and conclusion.

2. STOCHASTIC STATE SWITCHING AND EQUILIBRIUM ARRANGEMENTS

Experimental studies over the past decade have revealed unavoidable stochastic fluctuations in the levels and activities of biological circuits. Consequently, the behaviour of even cells with identical genetic material in a homogeneous environment can be quite different from one another. These stochastic fluctuations describe why transcription in both prokaryotes and eukaryotes is temporally discontinuous.

Cells show a wide range of stochastic state-switching between metastable states. A simple example of such system is a double negative feedback loops which create a bistable system with two stable states. Excitable system which consists of combination of positive and negative feedback loops is another example. In noise-triggered excitable differentiation systems, the cells enter a state probabilistically but return to the previous stable state after a well-defined time.

2.1 Equilibrium arrangement

In small core biological network the type of feedback loops determines specific dynamical behaviour. For two and three dimensional systems, it is possible to categorise these behaviours in terms of the numbers, types and arrangements of their equilibrium points. Each of these behaviours contains a set of equilibria which can be stable (i.e., stable fixed node, stable spiral node, stable limit cycle) or unstable (i.e., saddle node, unstable node, unstable spiral node, unstable limit cycle). As depicted in Fig.1c, a bistable behaviour can contain two stable equilibria separated by an unstable saddle node. Similarly, different arrangements of stable or unstable equilibria can lead to oscillatory or excitable behaviour.

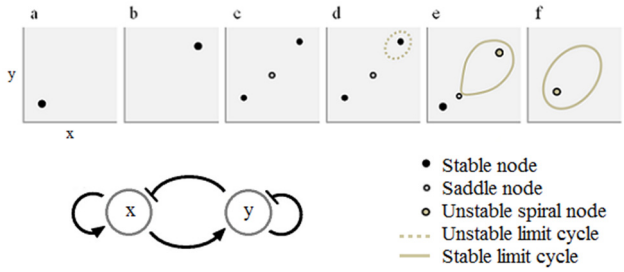

Fig. 1: A rich two-dimensional core network which has the capability to produce different behaviours including a and b) monostability, c) bistability, d) transition from bistability to excitability, e) excitability, f) oscillation.

One behaviour which has a major role in burst generation is excitability. In dynamical system terminology the rest state dynamic corresponds to the system residing at equilibrium (stable node, or a stable limit cycle or damped oscillation around a stable spiral node). Such large excursions exist in excitable systems because the quiescent state is near a bifurcation. This generality in types of equilibrium arrangements for small core networks (whether in neural or genetic circuits) raises two questions. The first question is associated with the topological similarity between the architectures of these core circuits and the second is related to the existence of particular equilibrium arrangements which are conserved during evolution.

2. BURSTING IN NEURAL CIRCUITS

Neurons can generate a series of pulses (burst) as a result of interplay between the fast ionic currents responsible for spiking activity and the slower currents that modulate it. Bursting activity has an important role in neural computation. Bursts are more reliable than single spikes, they facilitate transmitter release and have higher signal-to-noise ratio than single spikes. Bursts encode different features of sensory input compared to single spikes and these can be used for selective communication (Izhikevich 2007).

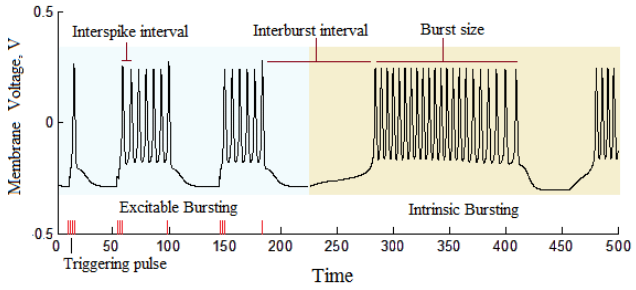

Fig. 2: Burst size or the interspike/interburst intervals encode the information in such impulse communication system.

There are two triggering mechanisms for generating bursts in neurons. The first mechanism involves excitable bursting, in which a stimulus triggers a neuron with a current that slowly drives it above the firing threshold. Fig. 2 shows the initiation and termination of bursting controlled by external triggering pulses. The second mechanism arises from manipulating the intrinsic properties of neurons. For example, a slow intrinsic membrane currents can modulate fast spiking activity. The currents build up during bursting leading to hyperpolarisation and finally termination of the burst. The current slowly decays during recovery and becomes quiescent, which allows the cell to fire another burst. These intrinsic currents (including Na^+, Ca^{2+} and K^+ currents) are controlled by specialised ion channels in the membrane. Therefore, one can imagine neurons can regulate their bursting properties by tuning the expression of genes which encode ion channels.

2.1. Refractory period in neurons

After each neural activation there is a refractory period which can be separated into absolute and relative refractory intervals. It is impossible to generate another pulse during the absolute refractory period; however, in the relative refractory period a neuron can generate another pulse with a strong enough stimulus. The dynamics of ion channels are

responsible for this refractory period. Sodium channels enter into an inactive state after an action potential. They cannot be made to open regardless of the membrane potential (absolute refractory period). Even after sodium channels have transitioned back to their resting state, a fraction of potassium channels remains open and membrane depolarisation is still difficult (relative refractory period). Due to the fact that different types of neurons have different densities and subtypes of ion channels, the duration of the relative refractory period is neuron-specific.

2.2 Types of excitability

Burst excitability plays a key role in modelling dynamical systems in neuroscience. In general, there are two types of excitable systems based on underlying bifurcations. Type I excitability happens when the stable state is near a saddle node on an invariant circle. In this type of excitability a neuron can fire all-or-none perturbations with an arbitrary low frequency. There is a well-defined threshold manifold and the excitatory and inhibitory perturbations produce different dynamical responses. Neurons act as integrators of incoming pulses. Therefore, a strong single perturbation or a series of small amplitude impulses with high enough frequency can excite the neuron and generate action potential.

In type II excitability the rest state has an oscillatory dynamic (spiral node). Therefore, the neuron fires in a certain frequency range due to the sub-threshold oscillation frequency. In other words, neurons act as resonator and based on the sub-threshold oscillation frequency they can be excited by inhibitory or activatory pulses with appropriate intervals. Types I and II of excitability can be used to design a neural communication system with amplitude and frequency modulations, respectively.

3.2.1 Biexcitability and bursting in a neural model

This section presents a neural model which embeds both types of excitability and produces bursts when triggered by external stimulation pulses. The neural model is a two-dimensional system of nonlinear differential equations (Morris–Lecar model of neuron):

$$\frac{dV}{dt} = I + g_{out}u(-0.7-V)+0.5(-0.5-V)+2W(-0.7-V) + g_{ca}F_1(1-V) \qquad (1)$$

$$\frac{dW}{dt}_{s} = F_3(F_2-V)$$

$$F_1 = 0.5\left(1+\tanh\left(\frac{V+0.01}{0.15}\right)\right), F_2 = \left(1+\tanh\left(\frac{V+0.1}{0.05}\right)\right),$$

$$F_3 = \frac{1}{3}\cosh\left(\frac{V-0.1}{0.1}\right)$$

Fig. 3 shows the biexcitability configuration in Morris–Lecar neuron model. The left-hand point (filled circle) is a stable fixed node and attracts all the trajectories. The middle point is a saddle node (open circle) and attracts the trajectories in one direction and repels them from other directions. There is a stable spiral point (rectangular node) surrounded by an unstable limit cycle (the bold cycle around the stable spiral node). The unstable limit cycle is also surrounded by a stable limit cycle. The trajectories inside the unstable limit cycle are attracted to the stable spiral node, and the trajectories outside it diverge to the stable limit cycle.

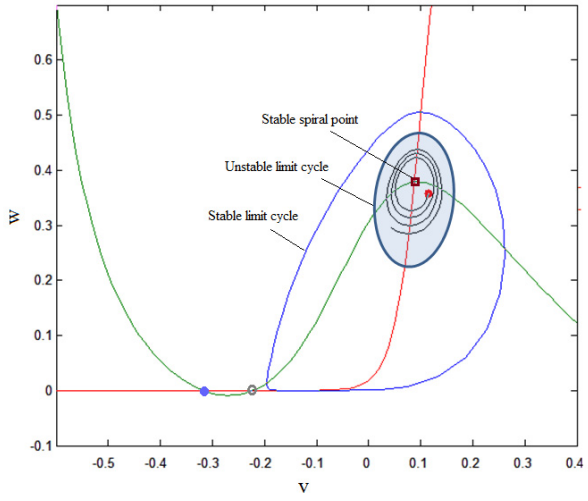

Fig. 3: Configuration of biexcitability in Morris–Lecar neuron model.

As depicted in Fig. 3, both types of excitability coexist in such equilibrium arrangement. Interestingly, switching between types I and II can only be achieved with external perturbations. The strength and frequency of the triggering pulses (red lines on the time axis in Fig. 4) and the current state of the system are involved in shaping burst patterns. When the triggering pulses are generated by a stochastic mechanism or noise it becomes more complicated to predict the response rigorously. One can imagine the same dynamic for genetic circuits in which the initiation of transcription is driven by a stochastic process.

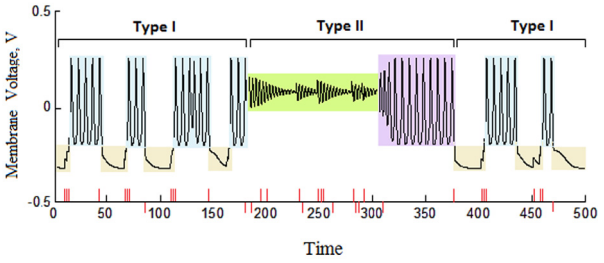

Fig. 4: Two types of excitability coexist in biexcitable configuration. Switching between type I and type II excitability in a neural model generates different burst patterns. When this system is in type I excitability, incoming pulses (red line on the time axis shows the incoming pulses) are integrated to achieve excitation and produce bursts. However, when the system operates as type II, the rest state has a sub-threshold oscillation and resonates with the input pulse frequency.

3. BURSTING IN GENETIC CIRCUITS

Similar to neural bursting, transcription occurs discontinuously. Transcription patterns show that active periods are followed by silent periods leading to transcriptional bursts (Suter, Molina et al. 2011). The discontinuous protein expression due to transcriptional bursts generates heterogeneity of protein accumulation in individual cells. This heterogeneity in protein expression could generate phenotypic diversity (Eldar and Elowitz 2010) and affect the probability of a cell entering a particular differentiation pathway (Suter, Molina et al. 2011).

3.1 Refractory period in transcription

A recent analysis (Suter, Molina et al. 2011) has revealed that the refractory period is not the same for all genes and therefore bursting kinetic is highly gene-specific. The steps involved in transcription machinery can explain why there is such a refractory period in the off state. It can be imagined that when the transcription machinery is in the elongation phase, a rapid biochemical event could disturb the transcriptional process and mRNA production. After that, preparing the transcription machinery to be active again requires several consecutive steps.

These steps include chromatin opening, of transcription factors binding(to the promoter and enhancer regions), the transcription machinery assembly, isomerisation, and escape from promoter proximal pausing (Suter, Molina et al. 2011). A recent analysis of 'on' and 'off' state transition times suggests two stages of refractory periods (off-1 and off-2) (Suter, Molina et al. 2011). The suggested off-1 and off-2 refractory periods in transcription kinetics can be compared with the absolute and relative refractory periods in neural dynamics.

3.2.2 Biexcitability and bursting in a genetic circuit

Different pieces of research on distinct genetic circuits have stated that they are topologically similar to excitable neural dynamics. Examples of genetic excitable systems are stress-driven competence in *B.subtilis* (Suel, Garcia-Ojalvo et al. 2006) and the P53 signalling network (Batchelor, Loewer et al. 2009). The differentiation of *B. subtilis* cells into competence is an ideal model system for studying the excitable dynamic due to the fact that the components and their functions are relatively simple and are well understood.

This circuit comprises ComK and ComS as a master regulator of competence and stress monitoring proteins, respectively, and MecA as a protease adaptor protein. ComK and ComS interaction is based on a Hill function and the enzymatic degradation reactions are assumed to be standard Michaelis-Menten ones.

By denoting the ComK and ComS protein concentrations with K and S, respectively, and by denoting the concentrations of free MecA and of the complexes MecA-ComK and MecA-ComS, an ODE model of interaction can be constructed. The role of MecA is represented by δ_k and δ_s, which correspond to the competitive enzymatic degradations of ComK and ComS providing that the total amount of MecA is assumed to be constant. By considering both basal expressions (b_k and b_s), and linear degradation (λ_k and λ_s) due to dilution (Detailed information about the biological components of this circuit can be found in (Suel, Garcia-Ojalvo et al. 2006)), the equation of the system is:

$$\frac{dK}{dt} = b_k + \frac{\beta_K K^n}{K + K^n} - \frac{\delta_k K}{1 + \frac{K}{\gamma_k} + \frac{S}{\gamma_s}} - \lambda_K K$$
$$\frac{dS}{dt} = b_S + \frac{\beta_s}{1 + \left(\frac{K}{K_s}\right)^p} - \frac{\delta_s S}{1 + \frac{K}{\gamma_k} + \frac{S}{\gamma_s}} - \lambda_s S \qquad (2)$$

The following table shows the model parameters values:

Table 1: Parameters of the competence system

b_k	0.0030 Molec/s	β_k	0.0506 Molec/s	k_k	100 Molec
b_s	0.0 Molec/s	β_S	0.0570 Molec/s	k_S	110 Molec
δ_k	0.0014 s^{-1}	γ_k	500 Molec	λ_k	0.0001 s^{-1}
δ_s	0.0014 s^{-1}	γ_s	50 Molec	λ_s	0.0001 s^{-1}

This system is rich enough to generate different types of behaviours including monostability, bistability and excitability, and limit cycle oscillation. The parameters of the system are explored to check if this circuit can produce biexcitability (Table 1, Hills coefficients: n = 2 and p = 5).

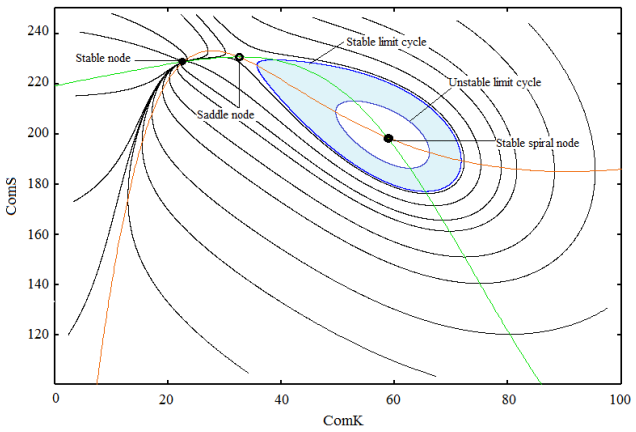

Fig. 5: Biexcitability in competence model. The equilibrium arrangement is similar to Fig. 3 in which two types of excitability coexist. The difference is that in the competence model the shapes of the nullclines are anti-correlated compared to Fig. 3.

Fig. 5 shows a phase portrait of an excitable competence system. Similar to Fig. 3, the red and green lines denote the nullclines of ComK and ComS, respectively. As depicted in the figure, this configuration is the same as Fig. 3 and represents the biexcitable dynamic. In this configuration, there is a stable node which represents the rest state (left intersection point) and a stable spiral point which represents

the competent state (right intersection point). The third point is an unstable saddle node (middle intersection point), which defines the threshold and intertwines the attraction and repelling domains of the other two nodes. The stochastic nature of genetic circuits provides a rich source of such perturbations. The difference between these two excitable systems is that in the competence model (Fig. 5) the shapes of the nullclines are anti-correlated compared to those in Fig. 3. Therefore the values of ComK and ComS change anti-correlated.

4. BURSTING IN SYNTHETIC CIRCUITS

Inspired by natural systems, synthetic decision-making circuits are gene regulatory networks which are triggered by specific environmental or cellular signals (Lim 2010, Morris, Saez-Rodriguez et al. 2010). From an engineering perspective, it is crucial to understand and compare the natural design principles by which biological systems have evolved and the engineering design principles used to construct man-made systems. Synthetic biology applies bottom-up constructive approaches to design new biological circuits. Based on dynamical properties and structures, each circuit has the potential to produce different behaviours which can encode a specific decision; one of the main challenges synthetic circuit designers face is the selection of appropriate design principles to link behaviours to decisions.

In this section a feedback structure (Fig. 6, III) which can produce different behaviours including monostability, bistablity, excitability or oscillation will be reanalysed. This structure has been used to design a synthetic oscillator (Stricker, Cookson et al. 2008). However, this circuit is rich enough to allow the implementation of additional functionalities such as synthetic pulse or burst generator. The synthetic circuit oscillator (Stricker, Cookson et al. 2008) was designed based on the structure depicted in Fig. 6. In this circuit, the genes araC and lacI have the same hybrid promoters Plac-ara1. In the presence of arabinose, the hybrid promoter is activated by AraC and in the absence of IPTG repressed by LacI; araC and LacI have a positive and negative self-regulation, respectively.

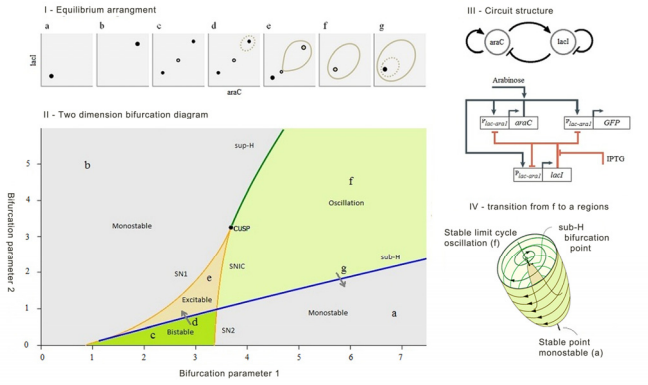

Fig. 6: A rich structure which has the potential to produce different behaviours. I) equilibrium arrangements show different possible stable and unstable equilibrium arrangements in phase space. II) Two dimensional bifurcation diagram shows how parameter space is separated by different dynamical behaviours. III) The structure of the synthetic oscillator (Stricker, Cookson et al. 2008). IV) Transition between oscillatory behaviour (f) to monostable (a) is through a temporal dynamic (subcritical Hopf (sup-H) bifurcation) controlled by slightly changing bifurcation parameter (arabinose in (Stricker, Cookson et al. 2008)).

The two dimensional bifurcation diagram (Fig. 6, II) shows how different behaviours partition the parameter space. Each of these behaviours was mapped to a specific number, type and arrangement of equilibria, which are depicted on the top panels, alphabetically (Fig. 6 I).

Different types of models have been introduced to characterise this structure (Smolen, Baxter et al. 1998, Hasty, Dolnik et al. 2002, Stricker, Cookson et al. 2008). A detailed model (Stricker, Cookson et al. 2008) was developed and analysed via stochastic simulations to characterise its behaviour. The authors' interpretation of the simulations was hindered by the presence of a bimodal oscillation which consisted of two stable oscillations (Supplementary Fig. 16 C (Stricker, Cookson et al. 2008)). However, this bimodal oscillation can be interpreted as a transient process from oscillatory (f region in Fig. 6. II) to monostable region (b region in Fig. 6 II). In this transient phase the system consists of one stable large amplitude and long period limit cycle which surrounded a smaller amplitude unstable limit cycle and a stable spiral node in the middle as depicted in panel g in Fig. 6 I. Part IV in Fig. 6 shows the transition from regions f to a via a subcritical Hopf (sub-H) bifurcation by changing arabinose.

Therefore, instead of the two stable limit cycles, there is only one large amplitude stable limit cycle which surrounds an unstable limit cycle. This unstable limit cycle separates the inner region of the large limit cycle. All the trajectories outside the unstable limit cycle oscillate to reach the larger stable limit cycle and all the trajectories inside the unstable limit cycle oscillate to reach the stable spiral node at the centre as depicted in Fig. 6, IV and Fig. 6 I g. In other words, the unstable limit cycle separates the basin of attraction of two stable behaviours which are a large amplitude limit cycle and a stable spiral node at the centre.

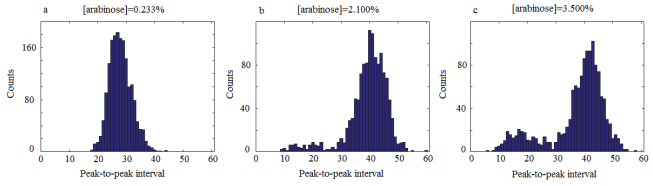

Fig. 7: Histograms of peak-to-peak intervals for the stochastic model of the synthetic oscillator (reproduced from (Stricker, Cookson et al. 2008), Supplementary Fig. 16). a) Distribution of peak-to-peak intervals is unimodal for the low arabinose level. b) for higher level of arabinose concentration (above 1.83%) the system shows bistable oscillations and switches between the two forms of oscillation stochastically. c) for higher level of arabinose the time interval in which the system produces low amplitude oscillation is increased.

As depicted in Fig. 6 II, to see this transient dynamic, the bifurcation parameter (arabinose) should be tuned precisely to be in the boundary of regions f and a. It is rarely if ever seen this transient dynamic in simulations and also one can imagine how it is difficult to see this in experimental results. Indeed, this behaviour was never observed experimentally (Stricker, Cookson et al. 2008).

5. DISCUSSION AND CONCLUSION

In this paper we have compared the architectures of three systems with different components and connectivity which can generate bursting behaviour. We have seen that although the biological mechanisms and molecular components in transcription and neural bursting are entirely different, the architectures and topologies of these circuits are comparable.

The bursting dynamic in neuroscience is modelled by a slow-fast system in which two subsystems with different timescales are coupled to each other. The fast subsystem is responsible for fast spiking and the slow subsystem modulates it. After each neural activity there is a refractory period which is divided into absolute and relative periods. Due to variations in the distribution and types of ion channels between different types of neurons, the relative refractory period and thus the inter-spike/inter-burst intervals are neuron-specific.

Similar to neural bursting, transcription appears to occur during short time periods (bursts) followed by silent periods. Such gene-specific refractory periods are similar to the neuron-specific refractory period which controls the characteristics of bursting in both systems.

In the fast-slow model of bursting, the slow subsystem often consists of activation and inactivation gates of slow currents. The steady-state activation and inactivation functions in neural model are represented by the sigmoidal shape, which is similar to the Hills function in genetic networks. Interactions between the inward and outward currents and the activation and inactivation gating mechanism create positive and negative feedbacks in the neural system. There are similar mechanisms which create positive and negative feedback loops in genetic circuits. For instance, the role of sis or trans regulatory elements, which can activate or inhibit transcription, is similar to the activation and inactivation gating mechanism in neural system (Tian, Zhang et al. 2009).

We have seen that a simple neural model which embeds both types of excitability produces different shapes of bursts when triggered by external stimuli (Biexcitability). This system shows bursting which is governed by an excitable deterministic dynamic triggered by a stochastic mechanism. We have seen that the analogous genetic competence system has the same topology and can show biexcitability for the selected parameter values.

Reanalysing a synthetic circuit which is designed to perform oscillation also reveals the capability of this feedback system to generate more sophisticated dynamical behaviours like bursting. For a specific range of parameters this circuit also can generate a dynamical which involves two oscillatory behaviours as has been seen in bimodal peak-to-peak distribution of stochastic simulation (Fig. 7). Comparing the natural design principles in neuroscience and genetics can be used as a way of choosing the appropriate design principle in synthetic biology. Analysing and constructing these minimal toy networks leads to an interrogation of the design principles of diverse systems. Moving towards increasing our understanding of how these small modular systems work has led to the application of synthetic biology.

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