



# MATHEMATICAL MODELLING AND COMPUTATIONAL BIOLOGY GROUP

## CENTRE FOR CELLULAR & MOLECULAR BIOLOGY, HYDERABAD, INDIA



The Mathematical Modelling and Computational Biology Group at the Centre for Cellular & Molecular Biology, Hyderabad has been working on theoretical studies of different areas in biology since 1983. The primary interest of this group is to understand and identify the generic mechanisms that underlie the formation and evolution of spatiotemporal patterns at different levels of biological organisation – from ecological to genetic. We use theoretical concepts and techniques to study complex biological processes, and aim towards the development and design of new properties of the systems, correction of pathological states, and prediction for improved functions. Our work primarily focuses on –

(a) **Intracellular Processes**, (b) **Pattern Formation and Collective Behaviour**, and (c) **Ecological Processes in Single and Interacting Species & Epidemiological Studies of Disease Data**.

**MODELLING INTRACELLULAR PROCESSES:** A variety of processes involving genetic and metabolic pathways govern the functional behaviour of cells. To understand and describe the dynamics and regulation of these processes, we study evolutionary processes acting at the genome level, and dynamics of real and model pathways.

**MODELING PATTERN FORMATION & COLLECTIVE BEHAVIOUR:** Living systems are spectacular examples of spatiotemporally organized structures. During development of complex organization there is dynamic equilibrium between the local and global processes acting at the intra- and inter-cellular levels in multiple space and time scales. We have studied - Pattern formation during development; Role of space, interaction strength and local dynamics in synchronization of spatiotemporal dynamics in multi-cell systems; Controlling spatiotemporal dynamics; etc.

**MODELLING ECOLOGICAL AND EPIDEMIOLOGICAL PROCESSES:** Here we have studied discrete population growth models for single and interacting populations; metapopulation dynamics under ecological processes; and spatiotemporal analysis of disease data.

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**MODELLING INTRACELLULAR PROCESSES**

**Comparative Genomics** Background: Focus and Objectives:

Complex regulatory mechanisms operate at genomic level to process the information embedded inside the sequence of bases in the genetic material. Increasing number of genome sequences and their characteristic pattern of codon (tri-nucleotide sequence coding for a particular amino acid) usage help us to study and compare and model the evolutionary phenomenon operating at the genomic level in different organisms.

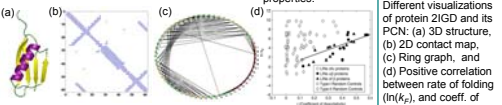
**Major Results:** **Horizontal Gene Transfer:** Using bioinformatic and statistical techniques we modelled and analyzed the *Tryptophan* biosynthetic pathway genes in a diverse group of microbial genomes to document their evolutionary history, and documented molecular taxonomic grouping based on the events of gene fusion and gene splitting.

**Codon Adaptation in Parasites:** Using multivariate statistics on Human Immunodeficiency Virus 1 (HIV-1) gene sequences over a period of 23 years, we found that the pattern of codon usage in HIV-1 genes exhibit differential translational selection towards its human host

**Algorithm developed:** **Variability Analysis of Multiple Alignment (VAMA)**  
A software for calculation of position-specific variability in multiple alignments of amino acid sequences, based on a simple symbol frequency score that considers the amino acid diversity.

**Protein Contact Networks** Focus and Objectives:

The global and local network parameters can be used to study similarities and differences in proteins from different structural classes ( $\alpha$ ,  $\beta$ ,  $\alpha/\beta$ , etc.). The 2D Boolean symmetric matrix (Contact map) and different network parameters offer insight into the overall structural organization (fold), which can be correlated to different biophysical properties.



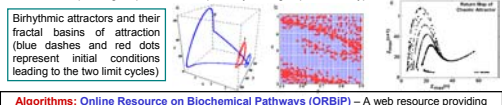
**Results:** Irrespective of their structural classes, all proteins show "Small World" property. The PCNs show assortative mixing at both short and long length scales. The long range network (LfN) of single state folding proteins show positive and negative correlation of their assortativity and clustering coefficient respectively to their experimental folding rates. PCNs have specific regions/groups of contacts that correspond to distinctive structural elements and the general network parameters can offer insight into the distinct arrangements of secondary structural elements in proteins showing evolutionary relatedness.

**Publications:** P. Barah and S. Sinha, *PRAMANA: Journal of Physics*, 2: 369 (2008). G. Bagler and S. Sinha, *Bioinformatics*, 23: 1760 (2007). G. Bagler and S. Sinha, *Physical A*, 346: 27 (2005).

**Regulatory Networks in Biochemical Pathways** Focus and Objectives:

Background: Biochemical reactions underlie cellular functions. The variety of functional dynamics is a consequence of nonlinearities inherent in multiple modes of biochemical regulation. These reactions utilize single and multiple negative/positive feedback processes as the primary mode of regulation to coordinate and control the pathway dynamics.

**Results:** Negatively auto-regulated pathways, as in the *Tryptophan* biosynthetic pathway, are stable for a large range of parameter values. Oscillations can be induced by reducing gene repression, enzyme inhibition and end-product utilization. Conditions are obtained for overproduction of *Tryptophan*. Propagation of reaction noise/perturbation in a multi-step negatively auto-regulated pathway depends on the extrinsic stochasticity, topology and the inherent dynamical state. A minimal pathway with coupled positive and negative feedback is capable of showing a range of dynamics – equilibrium, periodic, complex, biphymic, and chaotic. Biphymic behavior consists of two coexisting attractors with widely differing frequency and amplitude. The basins of attraction of the two attractors are fractal (Figure). The same pathway can show both sensitive or robust behaviors depending on parameters of pathway, strength, phase and type of noise.

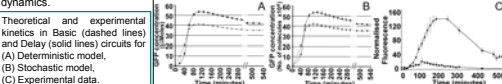


**Algorithms:** Online Resource on Biochemical Pathways (ORBP) – A web resource providing experimental, bioinformatics and theoretical information on biochemical pathways.

**Publications:** R. Maitheyre and S. Sinha, *Physical Biology*, 4: 48 (2007). R. Maitheyre and S. Sinha, In: "Function and Regulation of Cellular Systems: Experiments and Models", Birkhauser, Basel, 251-257 (2003). C. Suguna and S. Sinha, *Fluctuation and Noise Letters*, 2: L313 (2002). C. Suguna, R. Maitheyre, S. Suthram and S. Sinha, In: "Recent Research Developments in Biophysical Chemistry" (ISBN: 81-7736-116-3), Research Signpost, 91 (2002). C. Suguna, K. K. Chowdhury and S. Sinha, *Physical Review E*, 60: 5943 (1999). S. Sinha, *Biotech & Bioengng*, 31: 117 (1988). S. Sinha and R. Ramaswamy, *J. Theor. Biol.*, 132: 307 (1988). S. Sinha and R. Ramaswamy, *BioSystems*, 20: 341 (1987). S. Sinha and R. Ramaswamy, In: "Chaos in Biological Systems", Plenum Press, 69 (1987).

**Gene Circuits** Background: Focus and Objectives:

Two common motifs in the design of genetic and metabolic reactions networks are negative feedback aiding homeostasis, and multiple steps introducing delay in the formation of functionally useful end-product. While negative feedback helps to induce noise-reduction and robustness against perturbations, time delays are known to produce instability leading to oscillations or transient dynamics.



**Major Results:** Two simple pathways, with and without delayed repression, designed and constructed and cloned in *E. coli*. *Basic circuit* is a promoter-repressor pathway, and the *Delay circuit* contains a length of DNA (delay element) placed before the repressor gene - with GFP as fluorescence reporter of the circuit activity. Both deterministic and stochastic models predict the Delay circuit to show a transient overshoot in gene expression followed by gradual decline to steady state, which is exhibited by the experimental gene circuit (Figure). Population of cells with Delay circuit shows increased heterogeneity in gene expression – also shown in modeling studies. Overshoot with higher heterogeneity is useful in longer pathways.

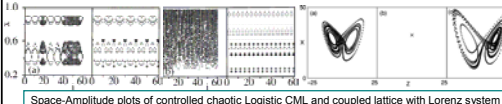
**Publication:** R. Maitheyre, R. R. Sarkar and S. Sinha, *PLoS ONE*, 13(3(8): e2972, (2008).

**MODELING PATTERN FORMATION & COLLECTIVE BEHAVIOUR**

**Coupled Map Lattice Models of Spatiotemporal Systems:**

Background: Spatially extended systems are commonly described using coupled map lattice (CML) models which exhibit a variety of complex spatio-temporal behaviours including spatio-temporal chaos, for different levels of spatial coupling and nonlinearity in the local dynamics. CMLs are used in modeling excitable media in biology (e.g., cardiac, neural, or retinal tissue, metapopulations in ecology), where the coupled discrete nature of the media and the resulting spatiotemporal dynamics has significance in their functions. Alterations in normal functions can lead to pathological conditions, and thus control of spatiotemporal dynamics has major implications in biological functions.

**Focus and Objectives:** Control of spatially extended systems can have two different motivations: (a) control of full system by manipulating all or parts of it – useful to exert global control over the system in the event of its exhibiting undesirable dynamics, and (b) controlling only a localized spatial region, leaving the rest of the system unperturbed – useful where local control is required without interfering with other parts of the system. The aim is to develop novel, general, and simple methods to control spatiotemporal dynamics in CMLs by applying constant pinning in the spatial domain.



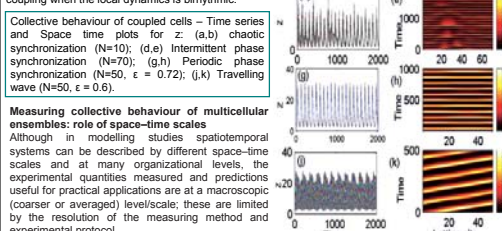
**Results:** Global and local control of spatiotemporal chaos can be achieved in CML models under different situations – uniform and non uniform pinning (Figures) with regular/random distributions, with spatial heterogeneity in local dynamics and coupling strength. The method is applicable to both chaotic and non-chaotic systems, with discrete and continuous local dynamics, and for different topologies of interactions. It can target dynamics towards both stable or unstable manifold, by changing the strength and the sign of pinning. It is easy to implement and does not require any a priori information of the system dynamics or explicit changes in its parameters.

**Publications:** S. Sinha, In: "Understanding Change: Models, Methodologies and Metaphors", Basingstoke: Palgrave Macmillan, 222 (2005). N. Parekh and S. Sinha, *Physical A*, 318: 200-212 (2003). N. Parekh and S. Sinha, *Physical Review E*, 65: 036227 (2002). N. Parekh and S. Sinha, In: "Nonlinear Dynamics and Brain Functioning", Nova Science Publishers, Inc. (New York, USA), (1999). N. Parekh, S. Parthasarathy and S. Sinha, *Physical Review Letters*, 81: 1401 (1998).

**Modelling Multi-Cell Systems** Focus and Objectives:

Background: Though biochemical reactions underlie cellular behaviour, collective spatio-temporal behaviour of a group of cells (tissue or cell population) can be quite different from individual dynamics of cells in isolation. For any dynamics to be observable in a multi-cellular environment, constituent cells have to show partially or fully synchronised behaviour.

**Results:** Each cell having an activator-inhibitor pathway exhibiting local chaotic dynamics shows collective emergent behaviour – partial to complete chaotic synchronization, travelling waves, and suppression of chaos to local periodic dynamics in the ring. Emergent behaviour depends on the initial conditions, size of the lattice (N) and strength ( $\epsilon$ ) of coupling when the local dynamics is biphymic.



**Measuring collective behaviour of multicellular ensembles: role of space-time scales**  
Although in modelling studies spatiotemporal systems can be described by different space-time scales and different organizational states, the experimental quantities measured and predictions useful for practical applications are at a macroscopic (coarser or averaged) length/scale; these are limited by the resolution of the measuring method and experimental protocol.

The spatiotemporal collective dynamics exhibited by the ring of cells is used to address if a multi-scale signature between, or be borne out by, the coarse-grained and averaged measurements done at different spatial and temporal scales. The role of spatial and temporal averaging of the variable of interest, z (endproduct of the pathway) at the different behavioural regimes. The spatiotemporal averaging of these "signals" in different synchronization states can have non-intuitive temporal features, and can either mask the differences, or show a totally different behaviour leading to inconsistent inferences. Such outcomes of measurements can lead to incomplete and incorrect understanding of physiological functions and pathogenesis in multi-cell ensembles from experimental data via a theoretical analysis.

**Algorithms:** Coupled Map Lattice Algorithm: Programmes in Fortran for simulating the dynamics of coupled systems

**Publications:** S. Rajesh and S. Sinha, *J. Biosciences*, 33: 289 (2008). C. Suguna and S. Sinha, *PRAMANA*, 71: 423 (2008). S. Rajesh, S. Sinha and S. Sinha, *Physical Review E*, 75: 011906 (2007). C. Suguna and S. Sinha, *Physical A*, 346: 15 (2005). S. Sinha and S. Mookerjee, *Developmental Biology*, 154: 218 (1992). S. Sinha, In: "Room of Differentiation", Neelkanth Publishers, New Delhi, 197-208 (1992). P. Grindrod, J. D. Murray and S. Sinha, *IMA J. Maths. Appl. Med. Biol.*, 6: 69-79 (1989).

**Spatiotemporal Dynamics in Metapopulation** Focus and Objectives:

Background: A metapopulation consists of subpopulations having non-identical behavioural and demographic properties, and occupying habitats of variable extirpation/colonization connectivity through migration. Spatiotemporal collective dynamics observed in the metapopulation scale may regulate local subpopulation dynamics. Functional dynamics of those species, which have the capability to induce damage to other species (e.g., a parasite or pathogen), assume larger importance in the metapopulation context, as their spread through space and time is dependent on the metapopulation behaviour.

**Major Results:** Homogeneous metapopulation, where all sub-populations have the same parameters, shows spatiotemporally synchronous dynamics in the long-term, independent of the exact forms of the dispersal function (Figure a).

Both landscape fragmentation and parametric heterogeneity (different attack rates of the parasite) in different sub-populations resist evolution of spatiotemporal synchrony, and the metapopulation remains asynchronous for a very long time (Figures b, c).

Long distance connections ("corridors") tend to induce synchrony. Evolution and maintenance of ecological and demographic diversity in nature seem to aid in species persistence at a metapopulation level.

**MODELLING ECOLOGICAL AND EPIDEMIOLOGICAL PROCESSES**

**Single Population Models** Background: Focus and Objectives:

One dimensional single lump discrete maps have been used to model single populations of species with non-overlapping generations (insects, annual plants). These maps display a "universal" bifurcation structure with increasing growth rate, where the population dynamics changes from stable to chaotic through the period-doubling route and the chaotic regime contains an ordered sequence of periodic windows. Due to their similarity, these models were used interchangeably in ecology. Though the models showed unstable dynamics, large number of field insect data showed predominantly stable dynamics. It questions the applicability of the models in real ecological situations.

Most species in nature interact with other species in a variety of modes – prey-predator, host-parasite, etc. – that influence their abundance and dynamics. Persistence and growth in such systems depend crucially on the population parameters such as the growth and predation/infection rates, ability of the prey to form refuge, and searching efficiency of the predator. Transmissible diseases are known to induce major behavioural changes in such systems by compartmentalising populations into susceptible, infected and recovered groups.

**Discrete single species populations:** Our study on different one dimensional maps showed that the universality in dynamics in the otherwise-thought-equivalent modes break down under small perturbations, such as constant migration.

The population dynamics depends on the nature of density-dependence in the maps. An unusual change of mode of extinction and survival where population growing beyond a critical rate can persist within a band of high depletion rates, whereas extinction occurs for lower depletion rates, was observed in the maps with long tails. We also showed that unstable dynamics in these models are suppressed under migration, thereby giving a possible reason why the field data showed predominantly stable dynamics.

**Interacting species populations – Prey-Predator & Host-Parasite systems**

Our eco-epidemiological model studies give a possible functional implication to the increased reports of viral infection in the planktonic community, and explains data on the occurrence of different patterns of phytoplankton "blooms" simply with a noisy viral infection rate. It does not need to invoke any specific system-dependent complex mechanisms for obtaining different types of "blooms".

The host-parasite model showing quasiperiodic dynamics exhibit regular dynamics with increased host migration (L).

**Publications:** S. Bhattacharya and S. Sinha, In: "Dynamics On and Of Complex Networks: Applications to Biology, Computer Science, Economics, and the Social Sciences", Birkhauser, (in press). B. K. Singh, J. Chattopadhyay and S. Sinha, *J. Theor. Biol.*, 231: 153-166 (2004). S. Sinha, *Current Science*, 73: 949-958 (1997). S. Sinha and P. K. Das, *PRAMANA*, 48: 87-98 (1997). S. Sinha and S. Parthasarathy, *Proc. Natl. Acad. Sci. USA*, 93: 1504-1508 (1996). S. Parthasarathy and S. Sinha, *Physical Review E*, 51: 6239-6242 (1995). S. Sinha and S. Parthasarathy, *J. Biosciences*, 19: 247-254 (1994).

**Life History Based Modelling of Insect Population** Background:

Predicting the dynamics of population size over many generations requires an integrated understanding of reproduction, growth, and mortality at the individual level, and density-dependent regulation through population-level processes such as competition, migration, and spatial structuring. For organisms such as insects, which have multiple life stages within a single generation (e.g., egg, larva, pupa, and adult), having different morphological, physiological and behavioural traits, present additional challenges as interactions between these life stages play a significant role in the regulation of the adult population size.

**Focus and Objectives:** To construct a life history based model to describe *Drosophila* population dynamics by considering the principal intra-generational regulatory processes between life stages.

**Major Results:** A two variable model has been developed which tracks the adult insect number and mean weight of the adult population at each generation by considering two major density-dependent effects of larval and adult crowding on the pre-adult survival and adult fecundity. The model shows good fit to laboratory data of *Drosophila* species.

**Modelling Infectious Diseases – Malaria & Leishmania**

Background: Microparasitic infections such as Malaria and Leishmaniasis (Kala-Azar) are major causes of human mortality in many areas of world, especially in the developing countries. The mechanisms responsible for the development of the disease in the host, and the spread of infection in a population are often complex and difficult to access. Mathematical models that simplify the real mechanisms, while maintaining the qualitative behavior of the process, are useful in understanding the transmission dynamics and principal underlying environmental and social factors.

**Focus and Objectives:** To construct and analyse mathematical and statistical models along with spatiotemporal disease prevalence data to study relationships between different environmental and demographic factors.

Variable selection through correlation study of causative variables and malaria incidence through non-linear curve fitting and testing the model predictions through ANOVA and Gauss-Markov models.

Developing a crucial early warning system for malaria incidence through suitable inputs to the model from already existing weather models.

Identifying important parameters relevant for an efficient control of infection and transmission of Leishmania using a biologically realistic model of human, animal and sand fly population.

**Major Results:** Regression models developed need no a-priori assumption about underlying parameters and yield good fits to the data sets of Malaria.

The methodology is applicable to different types of data sets and has predictive power in both temporal and spatial scales of data.

A good forecasting model can be prepared using inputs from already existing weather models.

Identification of key parameters in Leishmania infection are done.

A comprehensive spatiotemporal map of Malaria prevalence in India for 35 yrs have been developed.

**Algorithms/Tools:** Multi-step non linear polynomial regression method to model and forecast malaria incidence in Chennai, Tamil Nadu, India, and have used our method on three sets of malaria incidence, such as Slide positivity rates (all types of malaria, monthly data from Jan, 2002 to Jan, 2005), Total Plasmodium vivax deaths (Jan-Dec., 2006) and Plasmodium falciparum incidences and deaths (Zonal, Jan-Dec., 2006).

**Digitization Pro:** a fast, convenient and versatile tool to trace the contour boundary of a two-dimensional plot, useful in comparative visualization of numerical data as colour maps in cases like disease prevalence, population growth, etc.

**Collaboration:** Institute of Medical Biometry, University of Tuebingen, Tuebingen, Germany & Unit of Epidemiology, P.L. Institute of Tropical Medicine, Antwerp, Belgium

**Publications:** J. Chattopadhyay, R. R. Sarkar, S. Chaki and S. Bhattacharya, *Ecological Modelling* 177: 179-192 (2004).