MEG (Model Extender for Gepasi*): a program for the modelling of complex, heterogeneous, cellular systems*

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ABSTRACT

Summary: We describe a program for the construction of spatially distributed metabolic models, which may then be simulated using the metabolic simulator *Gepasi*. This is useful for the modelling of heterogeneous systems whether as liquid cultures or as spatially organised systems with specified interconnections.

Availability: MEG runs under Windows 95, 98, 2000 and NT, with either Intel or Alpha processors, and is available from http://gepasi.dbs.aber.ac.uk/softw/meg.html

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There is a substantial current interest in the simulation of metabolic systems (Giersch, 2000), especially for the analysis of their control structure (Fell, 1996). Such simulators allow one to specify the metabolic network and the kinetic parameters of the enzymatic or other catalysts involved. The model can then be run as a dynamic or steady-state simulation. The more sophisticated, such as *Gepasi* (Mendes, 1993, 1997), also allow one to effect numerical optimisation or fitting of model parameters to explain a set of observed variables (Mendes and Kell, 1998). However, such models to date incorporate a major implicit assumption (Kell *et al.*, 1989; Kell and Mendes, 2000), which is that all cells in the system are identical. Consequently such simulators cannot effectively deal with differentiated organisms and tissues, and even for unicellular suspensions it remains uncertain as to how bad the homogeneity assumption actually is (Davey and Kell, 1996; Kell and Mendes, 2000). Simulation is clearly an important approach to finding out. The program described here allows one to carry out both of these general types of simulation, and is integrated with the metabolic simulator *Gepasi*.

What MEG does is to take a 'base' *Gepasi* file as the input—which defines a single 'unit' of the metabolic system of interest—and produces a new one in which the

single unit is repeated in one of three general topologies. A 'unit' is best thought of as a cell, as it may itself contain more than one compartment. The output *Gepasi* file can then be run in *Gepasi* in the normal way. The three basic topologies are shown in Figure 1, and may be used to simulate a single-layer tissue, a liquid culture, or a tissue in a broth. Parameters may be copied exactly, or with a given random change in amplitude according to a uniform ($\pm x\%$) or normal distribution (with $x\%$ standard deviation), or with a 'positive normal' distibution (with $x\%$ standard deviation) in which all numbers must be positive. This allows the specific incorporation of heterogeneity under the control of the experimenter, while minimising the excruciating and time-consuming process of typing in large numbers of *Gepasi* models.

More specifically, MEG 'tags' all metabolite and reaction names with numbers that specify their 'spatial' position. The user has the option of specifying any number of metabolites which are transported between units.

The steps in using MEG, as explained in more detail in the program's Help file, are thus:

(1) Load a 'base' *Gepasi* model. MEG will display a window containing its details (Figure 2).

(2) Decide what topology you want for your multi-unit model (grid, soup or grid in soup).

(3) Decide the number of units your multi-unit model will have. If you have selected a grid topology then specify the number of rows and columns. If you selected a soup topology you enter the number of 'floating' units; the final model will have one extra unit (the external medium).

(4) If you selected a soup or 'grid in soup' topologies you should also decide if the reactions of the base *Gepasi* model also take place in the external unit (the 'medium'). By default MEG assumes that no reactions take place in the external unit.

(5) In most cases you will want some metabolites to be transportable between units. This is set through pressing the button 'Metabolite Mobility' which will

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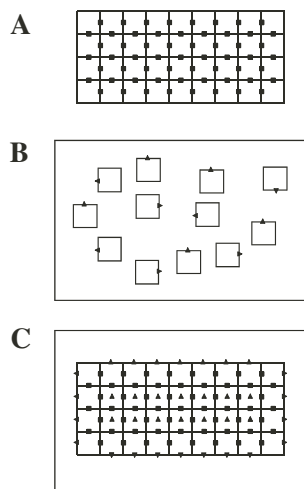
Fig. 1. The three topologies used in MEG. (A) Grid is an arrangement of units in a 2D rectangular grid, each unit communicates with at most 4 neighbours. (B) A soup topology is an arrangement of units in such a way that there is a special unit called external that is equivalent to a suspension medium. All other units can communicate only with the external unit, not directly between themselves. This resembles a liquid culture. (C) A 'grid in soup' topology is an arrangement of units in such a way that there is a special unit called external that is equivalent to a suspension medium and a series of other units arranged in a grid. Filled squares show where metabolites can be transported between units, filled triangles between units and the medium.

open a new window. This window presents a list of all the metabolites in the base *Gepasi* model.

(6) Heterogeneity. Unless you wish all units of your extended model to be replicas of the base *Gepasi* model, you have to decide which parameters are to be heterogeneous. MEG displays all the parameters of the base *Gepasi* model in the lower section of the main window (Figure 2).

(7) To create the new *Gepasi* multi-unit model, press the button 'Create' and give this file a unique name.

(8) Switch to *Gepasi* and load the multi-unit model newly created with MEG. You will see that this model now has a larger number of metabolites, compartments and reactions, as expected. These new items of the model retain the names from the original base model but have numbers appended identifying to which unit they belong. You can also change any parameter that you may like in this extended model. For example you may want one single unit to be different from all the others so you just change what you need to in the parameters of this unit. Note that MEG may also take this file as the input for the analysis of a yet higher level of hierarchical organisation.
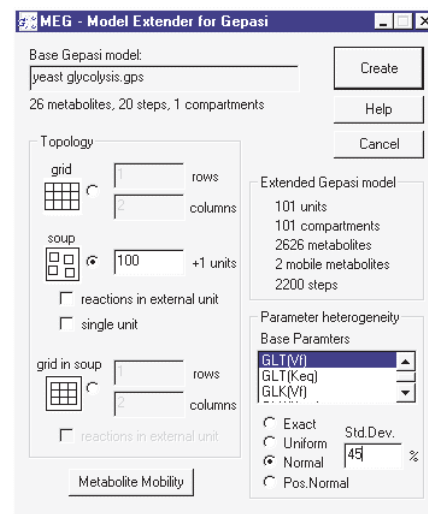

Fig. 2. The opening dialog box of MEG, showing the program's principal features.

In conclusion, MEG allows one straightforwardly to carry out metabolic simulations in which the properties of each individual cell may be differentiated explicitly. This approach could also be used for defining and simulating 2D reaction–diffusion systems.

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REFERENCES

Davey,H.M. and Kell,D.B. (1996) Flow cytometry and cell sorting of heterogeneous microbial populations: the importance of single-cell analyses. *Microbiol. Rev.*, **60**, 641–696.

Fell,D.A. (1996) *Understanding the Control of Metabolism*. Portland Press, London.

Giersch,C. (2000) Mathematical modelling of metabolism. *Curr. Opin. Plant. Biol.*, **3**, 249–253.

Kell,D.B. and Mendes,P. (2000) Snapshots of systems—metabolic control analysis and biotechnology in the post-genomic era. In Cornish-Bowden,A. and Cárdenas,M.L. (eds), *Technological and Medical Implications of Metabolic Control Analysis*. Kluwer, Dordrecht, pp. 3–25—see also http://gepasi.dbs.aber.ac. uk/dbk/mca99bio.htm.

Kell,D.B., van Dam,K. and Westerhoff,H.V. (1989) Control analysis of microbial growth and productivity. *Symp. Soc. Gen. Microbiol.*, **44**, 61–93.

Mendes,P. (1993) GEPASI: a software package for modelling the dynamics, steady states and control of biochemical and other systems. *Comput. Appl. Biosci.*, **9**, 563–571.

Mendes,P. (1997) Biochemistry by numbers: simulation of biochemical pathways with Gepasi 3. *Trends Biochem. Sci.*, **22**, 361–363.

Mendes,P. and Kell,D.B. (1998) Non-linear optimization of biochemical pathways: applications to metabolic engineering and parameter estimation. *Bioinformatics*, **14**, 869–883.