Supplementary materials showing the Forrester diagram structure of the models:

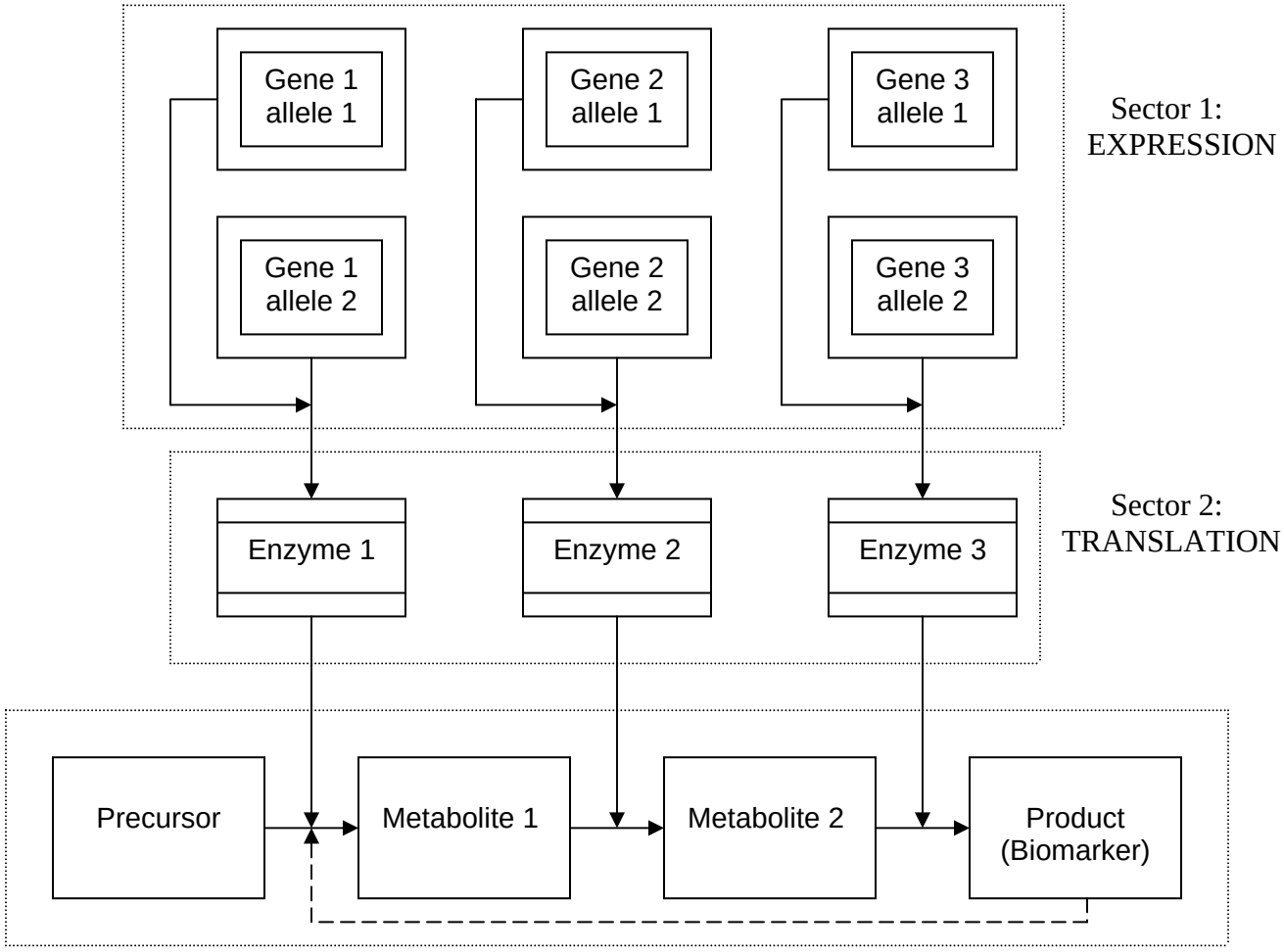

Figure 1 (reproduced from article). Schematic representation of the three enzyme linear cascade under investigation. Matter is conserved in each of the three sectors, with only information flowing between sectors (solid arrows). The EXPRESSION sector contains three genes, each with two alleles, which encode a specific enzyme in the pathway (depicted in the TRANSLATION sector). The CATALYSIS sector covers the conversion of metabolites from a precursor to a product in a three reaction linear chain. The concentration of the final product of the cascade, or "biomarker", is the outcome variable for our analysis. The dashed arrow (--) from product to the point of action of enzyme 1 represents the path of competitive inhibition (CI) engaged in the derivative model.

Figures 2-4 below depict the Forrester diagram outputs from STELLA (High Performance Systems), the software used for preliminary outlining of the models. The symbols used in these software-specific outputs are as follows. Clouds denote sinks of material outside the system, and rectangles are stocks, which are accumulators of specific materials. Thick arrows are flows, to represent transfer of material, and thin arrows convey information. Circles are converters, which pass constants to calculations. The rate of each flow is controlled by a converter. Flows may be fixed, or proportional to the level of a stock, in which latter case an information transfer arrow will link the appropriate stock and flow.

Figure 2

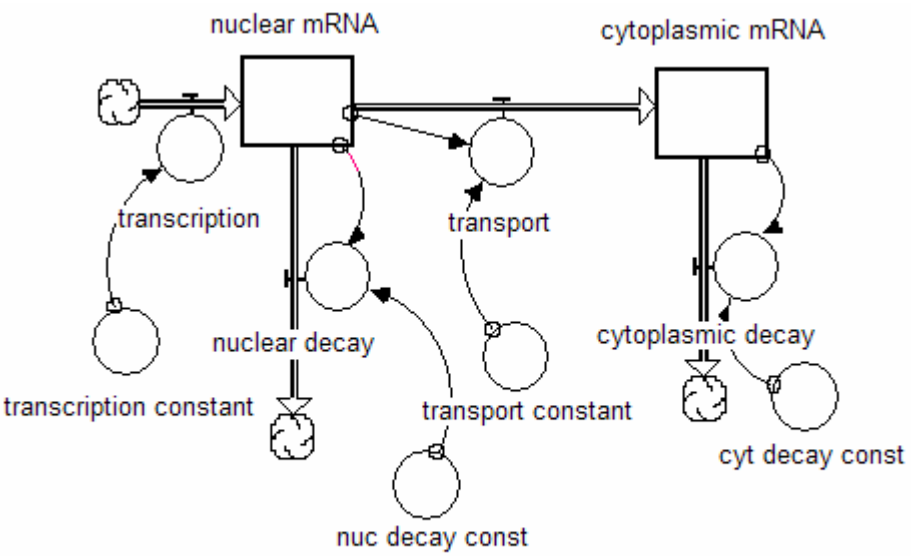

Figure 2. Forrester diagram of single allele model subunit. The allele boxes in Figure 1 all contain this model subunit.

Figure 2 shows the Forrester diagram for a single allele EXPRESSION subunit. Note that for each gene we have two of these subunits because we assume a diploid organism. All rate constants for gene expression, mRNA transport, enzyme decay etc. were taken from estimates published in Hargrove (1998) unless otherwise specified. Transcription takes place at a fixed rate dictated by the transcription constant (2.42×10^{-4} transcripts allele^{-1} s^{-1}), so that nuclear mRNA begins to accumulate, tracked in terms of copy number by the stock of the same name. This will decay at a rate equal to the product of its copy number and the nuclear decay constant (nuc decay const = 5.78×10^{-4} s^{-1}). All decay constants are directly related to the half-life time ($t_{½}$), whereby decay constant = $\ln(2)/t_{½}$. Thus, shorter half-life times imply higher decay rates. The nuclear mRNA will also be transported from the nucleus to the cytoplasm, in order to engage with ribosomes for translation. Transport occurs at a rate proportional to the copy number of nuclear mRNA and a transport constant (8.33×10^{-4} s^{-1}). The mRNA will then accumulate in the cytoplasm, tracked by the cytoplasmic mRNA stock, and decay at a rate equal to the product of its copy number and the cytoplasmic decay constant (cyt decay const = 9.64×10^{-5} s^{-1}).

Figure 3

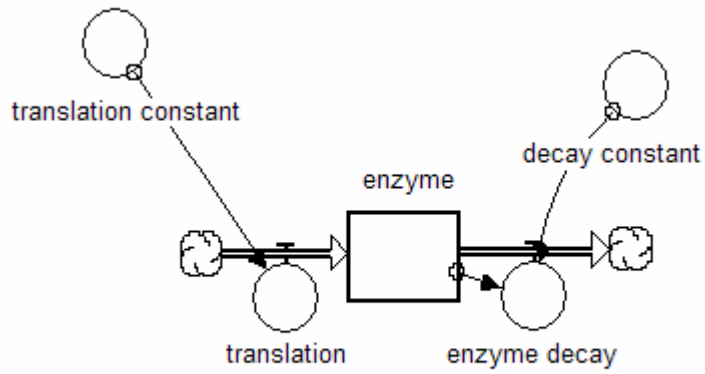

Figure 3. Single enzyme translation subunit. Information transfer arrows, not shown on this diagram, link the translation flow to the cytoplasmic mRNA stocks of the two alleles which encode the enzyme (refer to complete Forrester diagram also on website). The enzyme boxes in the Translation sector of Figure 1 all contain this subunit.

Figure 3 shows the Forrester diagram for a single enzyme TRANSLATION subunit. Translation is driven by the quantity of cytoplasmic mRNA specific for each enzyme in the EXPRESSION sector, whereby information transfer arrows (not shown) link the two appropriate cytoplasmic mRNA stocks (one per allele) to the translation flow. Translation is therefore equal to the product of the total quantity of cytoplasmic mRNA and the translation constant (0.028 s^{-1}). This calculation also involves the conversion of copy number to concentration, necessary for the following reason. Constants were available for transcription in terms of copy number per unit time, but the application of enzyme kinetic formulae in the final CATALYSIS sector requires units of concentration, for both enzymes and metabolites. Conversion was carried out by dividing the number of mRNA molecules by Avogadro's Constant (6.02×10^{23}) to yield the number of moles and dividing by the volume of cell mass in which the reactions were taking

place. The enzyme decays at a rate equal to the product of its concentration and a decay constant ($4.81x10^{-5}$ s^{-1}).

Figure 4

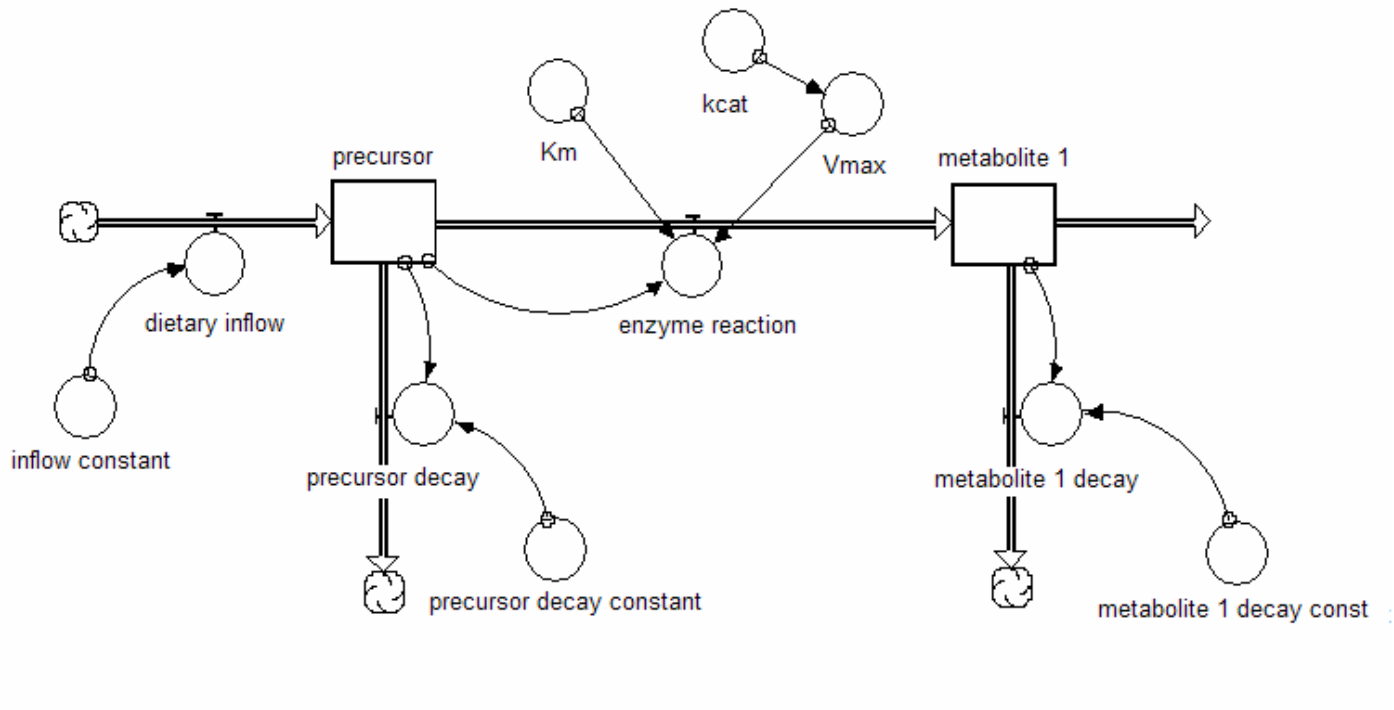

Figure 4. Single enzyme reaction model subunit. Information transfer arrows (not shown) link the Vmax converter with the appropriate enzyme (Fig 3). This diagram corresponds to the first enzymatic step depicted in the CATALYSIS sector of Fig 1.

Figure 4 depicts the Forrester diagram for part of the third and final sector, CATALYSIS. The precursor material flows in at a fixed rate, dictated by the inflow constant (100 pMs^{-1}) and accumulates in the stock of the same name. The rate of decay is equal to the product of precursor concentration and the precursor decay constant ($2.8x10^{-5}$ s^{-1}). The precursor is converted to metabolite 1 by enzyme 1, according to standard Michaelis-Menten kinetics.