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Examining and elucidation of human weight cycle model adopting e-cell simulation system

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Abstract:
Cellular rhythms regulate various physiological functions in circadian oscillatory mechanisms. Weight cycling or '*yo-yo*' dieting is an evitable process in human, because of subsequent loss and regain of body weight due to irregular diet. Human weight cycle (HWC) is the major factor for causing global epidemic diseases in human beings. Understanding the HWC process would provide potent additional knowledge to prevent obesity. However till date, there is no study dealing with examine the HWC model using virtual cell simulation based on system biological approach. Therefore, the present study was designed to develop a computational HWC model, which was simulated using E-cell system v3.0. The developed model has the cyclic feedback reactions of three significant variables (the consecutive cycles of weight loss in continuous food intake (Q) and regain of body weight (P) at highest threshold point of cognitive restraint (R)) which are obtained by mathematical modelling. The dynamic plot results supported that the PQR variables depicted sustained oscillation with reversible modification due to protein diet. By contrast, the virtual model simulation would provide extensive information on HWC, which might provide knowledge to develop HWC linked with obesity pathway. The presents study concludes that optimization of body weight is essential to prevent the obesity based diseases.

Key words: Human weight cycle (HWC) model, yo-yo diet, Goldbeter model, PQR, E-CELL system

Background:
The Rhythms bound with the biological system, involves network regulation as feedback loops at the cellular level. The molecular dynamics of the organisms are controlled by sustained oscillation in physiological functions of cellular rhythms and the biological oscillation hold systematic properties of regulatory interaction between metabolic/genetic networks of cell **[1].** Based on the view that post-translational regulation in the oscillatory mechanisms of Drosophila period protein (PER) phosphorylation is due to circadian oscillation, a theoretical model was examined for unraveling the molecular dynamics of the circadian rhythms **[2].** More quantity of food intake and less physical activity lead to energy imbalance and causes obesity (over weight gain) **[3].**

Obesity is the major problem to human health and cause many health risks like diabetes, hypertension, cardiovascular diseases etc. **[4].** As an initial factor, dieting leads to continuous loss and regain of body weight which is known as "*yo-yo*" dieting or weight cycling (WC). The human weight cycling process is determined through various metabolic and physiological effects such as body weight variability, morbidity and mortality **[5].** Also, body weight fluctuations can cause substantial changes in morbidity and mortality **[6].** Once a human reached

maximum level of overweight, reduction in food intake and fluctuation in weight oscillatory mechanisms occurs. The various physiological factors and their concentrations of kinetic values of human were confirmed by weight cycling mechanisms using experimental *in vivo* assessment together with theoretical analysis. Based on the evaluations, the mathematical model for weight cycling process was constructed, adopting feedback of the psychological nature in human. The model indicated the sustained oscillation levels in body weight are reflected through the significant kinetic parameters. The HWC process was demonstrated using theoretical and mathematical model (Goldbeter model) with significant PQR variables **[7].**

System biology is the most feasible approach in understanding computational models and its simulations of biological rhythms in human body systems **[1].** E-Cell is an object oriented generic software package used for cell system simulation using substance- reactor model **[8]** and the same cell system is used to analyze HWC oscillatory mechanisms in the simulation environment. The HWC model has major physical entities such as compartment (body) and species (body weight (P), dietary intake (Q), cognitive restraint (R) variables).

Therefore, the present study was carried out to examine the human weight cycling process and to elucidate the hypothesis by adopting E-cell system. Based on the Goldbeter model and extracted kinetic parameters datasets, we constructed a computational HWC model for virtual simulation and the hypothesis was examined by E-Cell. The present simulation study would provide knowledge to further understand HWC mechanisms in biological rhythms using other virtual environment.

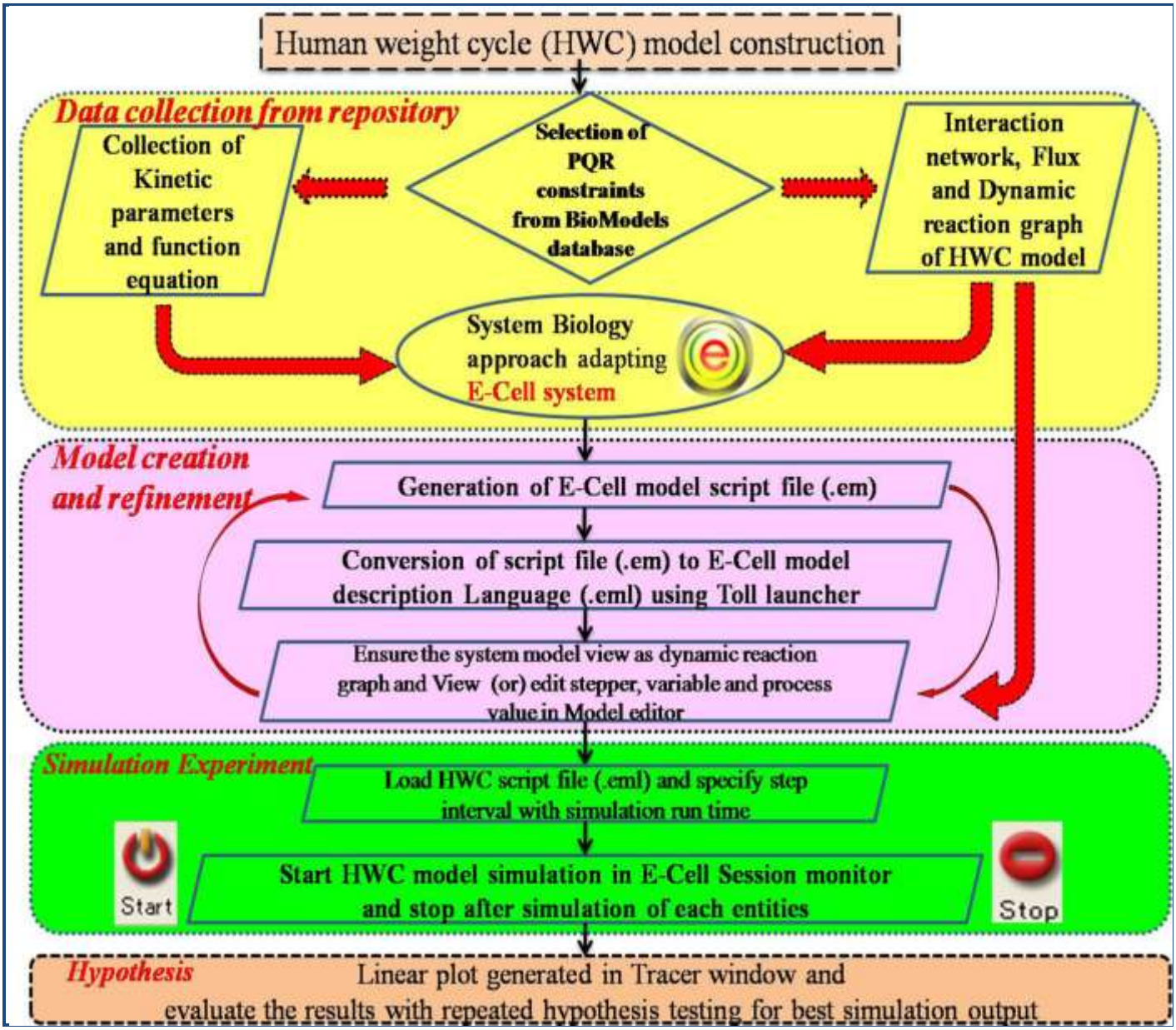

Figure 1: Schematic representation of virtual simulation using E-Cell system

Methodology:

Selection of HWC pathway

Human weight cycling was measured using mathematical modelling, and the physical entities of PQR constrains were retrieved from curated models of BioModels database (http://www.ebi.ac.uk/biomodels-main/) **[9].** The BioModels database provides consistent biological information with relation to mathematical equations used to understand quantitative models of cellular and metabolic reactions in living beings. The HWC model (BioModels ID: BIOMD0000000079) has a mathematical description of human body systems with annotated biological data sets. The whole continuous stepwise procedures were schematically represented using simulating HWC model **(Figure 1).**

Parameter collection for HWC model

The physical entities of HWC model have three major constraints viz. P, Q, R. The PQR constraints have valuable kinetic values represented by mathematical equations, and these were collected from curated with annotated models resources (BioModels database). Parameters of physical entities and their initial concentrations values were noted as 0.43, 0.8 and 0.55 for P, Q, R respectively **Table 1 (see supplementary material).** HWC model has variable with kinetic values based on the increase and decrease concentration of PQR constraints **Table 2 (see supplementary material).**

E-Cell simulation

Script files generation for HWC model

Although the mathematically annotated weight cycling model was reliable in directing the set of PQR constraints, now the kinetic and mathematical values of HWC model was generated adopting computational script file format. In E-Cell system, the body is known as compartment and the reaction type of system stepper, variable and process parameters were assumed as standard parameter in HWC model. The script file was saved as E-Cell model file (.em) format **[10]** (http: //ecell.sourceforge.net).

Conversion of script file

The E-Cell model script file (.em) was converted to E-Cell markup language file (.eml) format by using tool launcher (TL) module. Further, the .eml file was ensured like the dynamic reaction graph of weight cycling process were in the model editor (ME) module. The ME was used to view or edit system stepper, variable and process value to make reliable HWC model for simulation.

Load HWC model for simulation

Session monitor (SM) was used for loading HWC model from the parent directory and for visualizing the system variable with process parameters. Model selection file was showed in entity list window and the selected variable was viewed by property window. PQR constraints were selected individually using view selected option and modified variable value provided the significant simulation.

Simulation Output

Simulation reaction of HWC model and its PQR constraints were exhibited in tracer window. During runtime, the tracer window was used to trace the variables and processes of the model. The Y-axis and X-axis represents quantity with molecular concentration and time respectively.

Data analysis

The results were analyzed using Origin V.6.0 (http://www.originlab.com) and Microsoft Excel. Origin is graphical user interface (GUI) software used for the analysis of huge data and interpretation of scientific graphs.

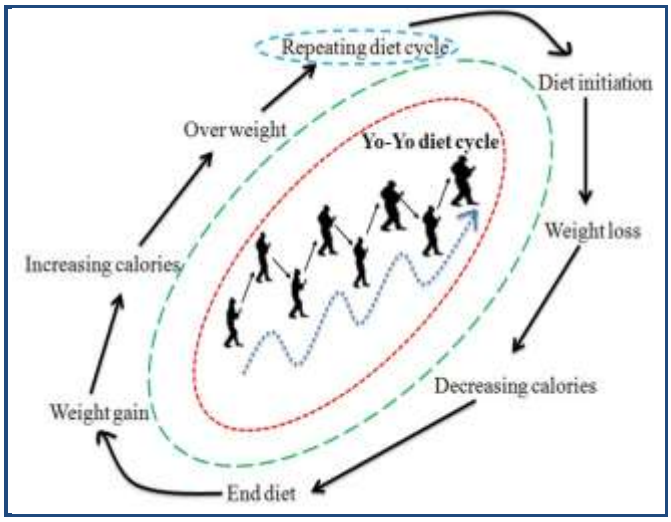

Figure 2: Graphical representation show the human weight cycle (HWC) has sustained oscillation during diet

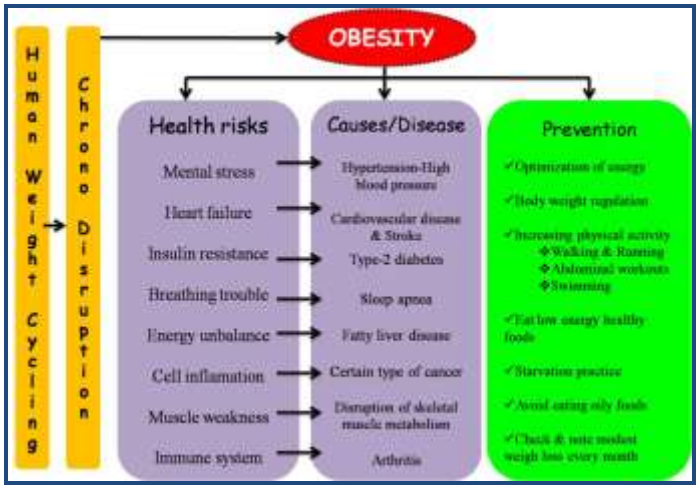

Figure 3: Diagram shows the health risk due to Chronodisruption and preventions for obesity

Discussion:

During diet, the sustained oscillation was observed due to loss and regain of repeated bout calories in body weight in human **(Figure 2).** HWC process is a major factor for causing obesity, which is developed due to chronodisruption metabolism. The chronobiological actions of melatonin have an important role in regulation of energy metabolism, energy balance and optimization of body weight **[11].** Obviously, chronodistuption can cause many health risks to human and its prevention process is showed in **Figure 3**. Digital information of the genome and the environmental cues generated from the biological information leads to understand system with predictable core of information **[12].**

System-level understanding of genes and proteins information is important to focus on comparison of system structure and their dynamics. Dataset of quantitative and qualitative information is required to develop a system model **[13].** The examination of cellular rhythms and their mechanisms are more useful to collect information about biological oscillation adopting system biological approach. Several models have been developed based on system biology including bacterial osmoregulation switch using E-Cell system, which deciphered the quantitative parameters of two component regulatory systems by virtual simulation method **[8].** Based on the extensive system biology approach, the HWC model was developed and simulated with specific step interval and run time. Schematic stepwise procedure used for performing the virtual experiments are showed in **Figure 1**. The dynamic reaction graph for HWC was obtained from BioModels database and it is developed using E-Cell system **(Figure 4A & 4B).**

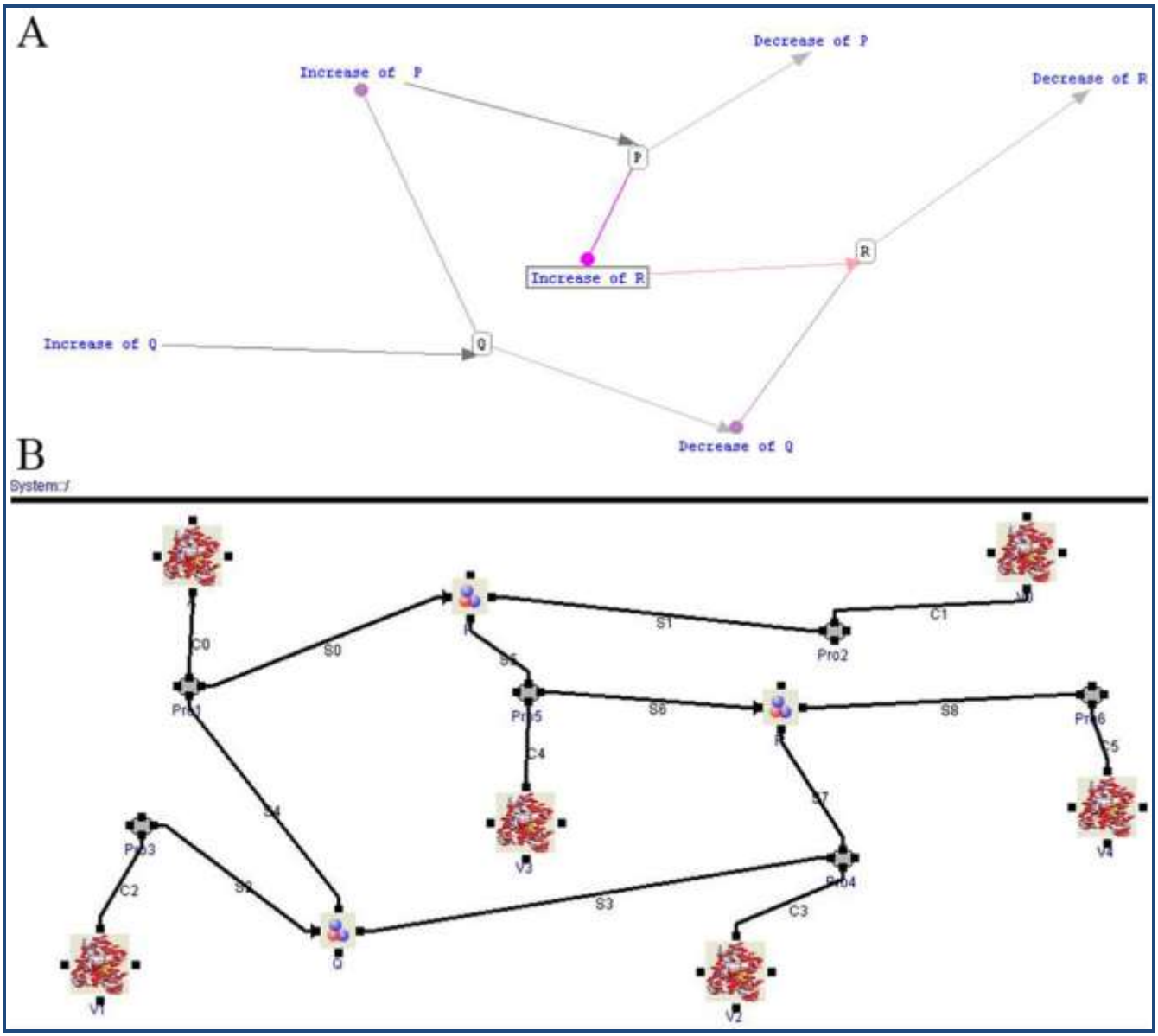

Figure 4: Construction of HWC model. **A)** Dynamic reaction graph obtained from BioModels database; **B)** The dynamic reaction graph developed using E-Cell with interlinkage of physiological-variables and process of HWC.

Virtual cell simulation in variables

Mass Action Flex Process and ODE23 stepper modules were used to build a HWC model with efficient parameter of WC process under virtual environment. The kinetic value of PQR consists of molar concentration, velocity and quantity. Synthetic oscillation was used to tune the parameters, which control the dynamics of the regulatory network. The artificial oscillation provides a path for pharmacological application such as monitoring of drug delivery methods to the system **[1].** During simulation, the identification of flux variation between variables is more important, which is useful to clarify the interlinked metabolic pathway and the kinetic properties of the network. Specific step interval along with thousand seconds runtime were used for simulating variables, and the fluctuations were represented as a linear graph in tracer window. The complete simulation traces were retrieved as

output of E-cell data (.ecd) file format in logger window (LW), which was stored as simulation results. The linear graph was developed by stimulating the PQR variables using the procedure showed in **Figure 5A**.

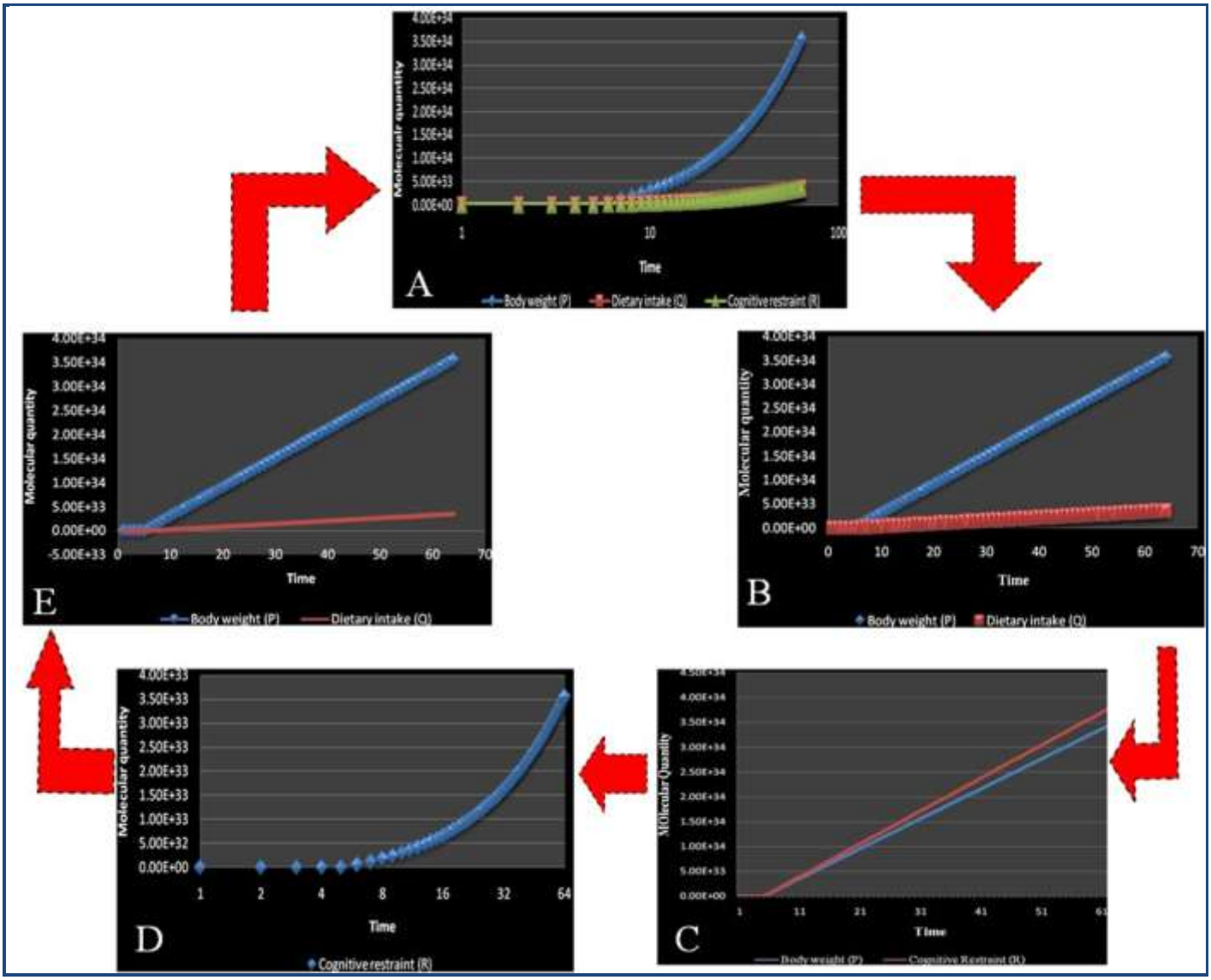

Figure 5: Simulation graph of weight (P), dietary intake (Q) and cognitive restraint (R). **A)** All the variables were simulated without numerical changes and retrieved as a linear graph; **B)** Variables P, Q was simulated using artificial numerical modification using simulation by manual method. The variable P was increased rapidly to reach a threshold level and Q showed downward linear plot due to reduction in food intake. C) Variable R was simulated manually and it was increased or decreased linearly while body weight exceeds the maximum.

Effect of body weight simulation

The body weight (P), a major variable compared to other physical entities, was selected in tracer window. The entity list window showed many property lists from virtually constructed HWC model, and the variables are mass action flex process function, quantity, molecular concentration and velocity. The script of HWC model was loaded in E-cell system and P was selected as 0.43 for initial concentration of simulation, whereas in artificial numerical simulation, the standard value of P (0.43) was multiplied by 100 and the numerical values of Q and R were standard. Interestingly, P values showed an increased linear static plot after stimulation **(Figure 5B & 5E)** which was then retrieved as an output file in tracer window. Therefore, the results revealed that the artificial simulation alone can adopt the changes in the body weight. The changes in body weight of human may be the cause for secretion of appetite stimulant hormone such as an orexigenic signal on ghrelin and other neuropeptides, which in turn may lead to increased food intake **[14].** In addition to ghrelin a long-term regulator of energy dissipation of plasma level in body **[15],** a variety of neuropeptides were also synthesized, which regulate the food intake.

Effect of dietary intake simulation

The artificial numerical modification was executed for dietary intake (Q) and the variable Q (0.8) was multiplied with 100; whereas P and R were as the same standard. The results showed a decreased linear plot **(Figure 5B & 5E).** These

changes may reflect on the secretion of gastrointestinal peptides such as glucagon and cholecystokinin, which could probably enhance the satiety and reduce the food intake in human **[16].**

Effect of cognitive restraint simulation

Cognitive restraint (R) value 0.55 was multiplied with 100, while P and Q remain in same standard values. The results showed that R has increased level with a linear plot, which is parallel to body weight **(Figure 5C & 5D).** The orexigenic and anorexigenic signals, which are involved in appetite control, may increase when an increase in cognitive restraint occurs; so that the body weight (P) may exceed the threshold level **[7].** Therefore, the present study concluded that the E-Cell is an efficient computational platform to design and construct virtual model based on system biology approach.

Conclusion:

The HWC process is the major reason for obesity in human, which leads to many disease and life risks. The computational simulation of human physiological parameter would reveal the changes in the body virtually. Therefore, in the present study, HWC simulation model was developed using E-cell based system biology approach with physiological factors such as food intake (Q) body weight (P) cognitive restraint (R). The results concluded the steady state threshold level of body weight dependence of R on P and Q on R. These physiological parameters were depended on each other and their fluctuation may cause obesity to human. The work further concluded that the E-Cell simulation system would be used to design and construct various virtual based system biology networks.

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References:

[1] Goldbeter A *et al. FEBS Lett.* 2012 **586**: 2955 [PMID: 22841722]
[2] Goldbeter A *Proc. Biol. Sci*. 1995 **261**: 319 [PMID: 8587874]
[3] Caixàs A *et al. Drug Des Devel Ther*. 2014 **18**: 1419 [PMID: 25258511]
[4] Must *et al. JAMA* 1999 **282**: 1523 [PMID: 10546691]
[5] Brownell KD & Rodin J, *Arch Intern Med.* 1994 **154**: 1325 [PMID: 8002684]
[6] Jeffery RW *et al. Am. J Clin Nutr.* 1992 **55**: 641 [PMID: 1550037]
[7] Goldbeter AJ, *Biosci.* 2006 **31**: 129 [PMID: 16595882]
[8] Srividhya KV & Krishnaswamy S, *BMC Microbiol.* 2004 **4**: 44 [PMID: 15571621]
[9] Li C *et al. BMC Syst Biol.* 2010 **4**: 92 [PMID: 20587024]
[10] Tomita M *et al. Bioinformatics* 1999 **15**: 72 [PMID: 10068694]
[11] Cipolla-Neto J *et al. J Pineal Res.* 2014 **56**: 371 [PMID: 24654916]
[12] Hood L *et al. Science*. 2004 **306**: 640 [PMID: 15499008]
[13] Kitano H *Science.* 2002 **295**: 1662 [PMID: 11872829]
[14] Wren AM *et al. J Clin Endocrinol Metab*. 2001 **86**: 5992 [PMID: 11739476]
[15] Wynne K *et al. J Endocrinol*. 2005 **184**: 291 [PMID: 15684339]
[16] Woods SC *Am. J Physiol Gastrointest Liver Physiol*. 2004 **286**: G7 [PMID: 14665437]

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Supplementary material:

Table 1: Physical entities in PQR model for human weight cycle

S. No	Physical Entities	Note	Compartment	Initial Concentration
1	P	Body Weight	Body	0.43
2	Q	Dietary Intake	Body	0.8
3	R	Degree Of Resolution Measuring Cognitive Restraint	Body	0.55

Table 2: A whole parameter in PQR model for human weight cycle

S. No	Physical Entities	Reaction Type	Parameter Value
1	**Increase of P**	Constant	a Value: 0.1
2	**Decrease of P**	Constant	**V:** 0.1 **Km:** 0.2
3	**Increase of Q**	Constant	**V1:** 1.0 **K1:** 0.01
4	**Decrease of Q**	Constant	**V2:** 1.5 **K2:** 0.01
5	**Increase of R**	Constant	**V3:** 6.0 **k3:** 0.01
6	**Decrease of R**	Constant	**V:** 2.5 **Km:** 0.01