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OXFORD

Gene expression

# A model for the expression of *gap* genes based on the Jeffreys-type equation

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## Abstract

**Motivation:** We propose the third-order model equation of the Jeffreys type for concentrations of *gap* gene proteins in order to take into account particle inertia. *Gap* genes are responsible for formation of body segments in *Drosophila melanogaster* embryo during its early development. Usually the expression of the genes is described by the model of protein transport based on conventional diffusion equation. However, the model is known to govern the Brownian (non-inertial) motion of particles; hence, it is hardly applicable to the description of protein transport.
**Results:** Analysis of the Jeffreys-type equation results in the necessary condition for the problem to be well-posed. Application of the Jeffreys-type equation with non-linear terms to description of the dynamics of *gap* gene network demonstrates better fitting to experimental data than the conventional model.
**Availability and implementation:** Implementation of solver algorithms and the software are freely available from: https://github.com/wswgG/solver-for-the-Jeffreys-type-equations-system
**Contact:** gula@mail.ioffe.ru
**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

## 1 Introduction

Segmentation genes play crucial role in early development of *Drosophila melanogaster*, being responsible for formation and positioning of body segments (Nusslein-Volhard and Wieschaus, 1980). The segmentation genes are divided into four classes: *maternal* genes, *gap* genes, *pair-rule* genes and *segment polarity* genes—according to their mutant phenotype (for details, see Nusslein-Volhard and Wieschaus, 1980). At present, *gap* genes have become popular investigation object, in particular, for system biologists due to the following reasons (Jaeger, 2011). First, the *gap* gene system is the most upstream regulatory layer among zygotic genes, controlling *D. melanogaster* embryogenesis and determining both the position and the identities of body segments. Second, availability of big amount of experimental data on gene expression enable to model mathematically and reconstruct the *gap* gene network *in silico* (Gursky *et al.* 2008; Jaeger *et al.* 2004; Reinitz *et al.* 1995).

Usually the gene expression is described by means of conventional model based on the parabolic reaction diffusion equation, written for an unknown protein concentration function $u(x, t)$ as:

$$u_t = D\,u_{xx} + R(x, t, u(x, t)), \tag{1.1}$$

where $x$ is space coordinate, $t$ is time, $D$ is the diffusion coefficient and $R(x, t, u(x, t))$ is a reaction term representing protein production and its degradation.

Equation (1.1) was proposed in (Mjolsness *et al.* 1991) for description of the dynamics of internal state of nuclei in blastoderm of *D. melanogaster* embryo and originally contained the diffusion term in discrete form. The model took into account three major processes essential for embryo development: synthesis of proteins, their

diffusion between nuclei and degradation. The same approach was used in (Driever and Nusslein-Volhard, 1988) to explain the dynamics of the Bicoid maternal protein in *D. melanogaster* embryo. It is known as the synthesis-diffusion-degradation model (Gregor *et al.*, 2007). The model equation (1.1) with diffusion term in continuous or in discrete form have been widely used in the last two decades for description of diffusive transport of proteins, e.g., synthesized by *maternal* gene *bicoid* or *gap* genes in *D. melanogaster* embryo blastoderm during early embryogenesis (Drocco *et al.*, 2012; Gregor *et al.*, 2005; Gursky *et al.*, 2004; Mjolsness *et al.*, 1991; Reinitz *et al.*, 1995).

However, (1.1) has a crucial drawback: it is based on the phenomenological Fick law for mass flux, which was formulated for Brownian motion of non-inertial particles, and, therefore, it is applicable only for description of light particles motion, for example, in an ideal gas. Proteins are heavy complex organic molecules, and for this reason, the classical approach is hardly applicable for modelling of protein transfer.

Mathematically, non-inertial description of inertial particle transport leads to an infinite velocity of disturbances propagation defined by (1.1). For example, when $R(x,t) \equiv 0$ and with initial condition $u(x,0) = \delta(x)$, where $\delta(x)$ is the Dirac delta function, the fundamental solution to (1.1) has the form:

$$u(x,t) = \left(1/\sqrt{2\pi t}\right) \exp\left(-x^2/4Dt\right), \tag{1.2}$$

and it is positive for any finite values of $x$, therefore a sudden change of a substance concentration somewhere will immediately transfer to any arbitrary point. The profile of (1.2) at certain time moment is shown in Figure 1a (see, e.g. Masoliver and Weiss, 1996; Sobolev, 1997; Weiss, 2002), and we call this phenomenon of an infinite velocity as 'the diffusion paradox' for brevity. Immediate disturbances propagation contradicts with experiments, in which proteins move in an embryo very slow, with the velocities about 1–5 μm/s (see Gregor *et al.*, 2005, 2007).

In 1948, Cattaneo proposed the telegraph equation, containing additional 'relaxation time' and, therefore, free from the diffusion paradox, to model mass (heat) transfer. The fundamental solution to the equation describes propagation of disturbances with finite velocity, but due to the wave-like behaviour it may reach negative values inappropriate from biological viewpoint. Furthermore, the fundamental solution to the telegraph equation with the Dirac delta function as an initial condition contains two discontinuous wave fronts, propagating in opposite directions.

In 1989, Joseph and Preziosi proposed the description of heat transfer based on the refined model for flux of rheological fluid in the Earth crust introduced in 1929 by H. Jeffreys. Similarly, one can obtain an equation for determination of mass transfer via elimination of the flux function from the mass balance equation:

$$u_t(x,t) = -J_x(x,t) + R(x,t,u(x,t)), \tag{1.3}$$

and the Jeffreys refined formula for flux:

$$J(x,t) + \tau J_t(x,t) = -(D + D_1)\, u_x(x,t) - \tau D_1 u_{xt}(x,t). \tag{1.4}$$

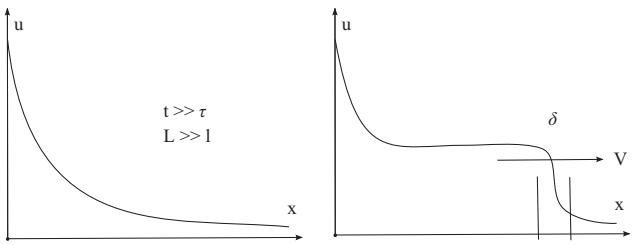
The resulting Jeffreys-type equation:

$$\tau u_{tt} + u_t - \tau D_1 u_{xxt} = (D + D_1)\, u_{xx} + R(x,t) + \tau R_t(x,t), \tag{1.5}$$

contains two additional parameters, as compared with (1.1), namely, the relaxation time $\tau$ and the second diffusion coefficient $D_1$, thus taking into account the particle inertia. The particular solution to (1.5) at certain time moment under the assumptions $R(x,t) = 0$, $u(x,0) = \delta(x)$, $u_t(x,0) = 0$ is shown in Figure 1b. It can be seen that a small amount of particles occurs at infinity, and the diffusion paradox for the Dirac delta function as an initial condition is not completely eliminated by the proposed model. However, even in this case the Jeffreys-type equation describes formation of a smooth wave front from an initial sharp discontinuity, that is always positive, and its propagation with finite velocity. Applications of the Jeffreys-type equation to different physical problems can be found in (Joseph and Preziosi 1989a,b; Rukolaine and Samsonov, 2013; Sobolev, 1997).

Due to similarity between heat and mass transfer both the telegraph equation and the Jeffreys-type equation are of interest for description of protein transport in biological systems. Nevertheless, the *maternal* and *gap* genes expression in *D. melanogaster* embryo is often modelled by means of the parabolic reaction diffusion equation, which limited applicability has been widely discussed (see Fort and Mendez, 2002; Masoliver and Weiss, 1996). The conventional model is still popular due to simplicity and similarity at large time scales of the fundamental solutions to all parabolic, the telegraph and the Jeffreys-type equations, as shown in Rukolaine and Samsonov, (2013).

In this article, we apply the mathematical model consisting of the coupled Jeffreys-type equations with non-linear reaction terms to study the dynamics of protein concentrations in gene network of four *gap* genes. The equations are solved numerically, and the results will be compared with experimental data and with numerical solution to the model based on the conventional diffusion Equation (1.1).




(a) solution profile of the parabolic equation

(b) solution profile of the Jeffreys type equation

**Fig. 1.** Profiles of the solutions to (1.1) and (1.5) without synthesis terms for $x > 0$ and the Dirac delta function $\delta(x)$ as an initial condition (Joseph and Preziosi, 1989b)

## 2 Methods

### 2.1 Model problem of dynamics of protein concentration

Consider the model problem of finding the distribution of proteins in an embryo, when *maternal* gene protein behaviour is described. According to the simplest model (Gregor *et al.*, 2005; Houchmandzadeh *et al.*, 2002), a protein of the *maternal* gene *bicoid* (*bcd*) diffuses through an embryo and decays uniformly with constant rate $\gamma$, therefore the reaction term $R(x, t)$ in (1.5) can be written as $-\gamma u(x,t)$. The embryo is assumed to have no mass exchange with an external environment. The protein is synthesized at the point source located near the anterior pole of an embryo, and the production rate is assumed to be constant in time (Gregor *et al.*, 2005, 2008), that leads to the boundary conditions:

$$(\mathbf{J}(x,t) \cdot \mathbf{n}_{in}(x))|_{x=0} = q, (\mathbf{J}(x,t) \cdot \mathbf{n}_{in}(x))|_{x=L} = 0, \tag{2.1.1}$$

where $\mathbf{n}_{in}$ is the internal normal, $q$ is the source intensity. Initial conditions are specified in general form:

$$u(x,t)|_{t=0} = \varphi(x), u_t(x,t)|_{t=0} = \psi(x) \tag{2.1.2}$$

Taking into account the continuity of $J(x, t)$ in $[0, L] \times [0, T]$ and constant flux at the domain boundary, the equation for flux, written for $x = 0$ and $x = L$, leads to the differential equations for functions $u_x|_{x=0}$ and $u_x|_{x=L}$, respectively, which depend on $t$. Initial conditions of the Neumann type for both equations can be obtained from (2.1.2) in a form:

$$u_x|_{x=0} = \left(\varphi_x(0) + \frac{q}{D_2}\right) \exp\left(\frac{-tD_2}{\tau D_1}\right) - \frac{q}{D_2} \tag{2.1.3}$$

$$u_x|_{x=L} = \varphi_x(L) \exp\left(\frac{-tD_2}{\tau D_1}\right), \; D_2 \equiv D + D_1. \tag{2.1.4}$$

We rewrite (1.5), now containing $R(x, t, u(x, t)) = -\gamma u(x, t)$, in the form:

$$\mathfrak{L} u - \beta u = 0, (x, t) \in [0; L] \times [0; T], \tag{2.1.5}$$

where $\mathfrak{L} = \varepsilon\partial_{tt} + \partial_t + \delta\partial_{xxt} - \alpha\partial_{xx}$ is the differential operator of the problem, the equation coefficients are $\varepsilon = \tau\chi$, $\delta = -\tau D_1\chi$, $\alpha = (D + D_1)\chi$, $\beta = -\gamma\chi$ and $\chi \equiv 1/(1 + \gamma\tau)$.

The Fourier method leads to the exact solution to the problem:

$$u(x, t) = w(x, t) + \sum_{k=0}^{+\infty} \cos(\pi k x/L)\, S_k(t), \tag{2.1.6}$$

where $w(x, t)$ is an auxiliary function, and both $w(x, t)$ and $S_k(t)$ are defined in Supplementary notes, available online.

## 2.2 Analysis of initial conditions

Integrating (1.3) with $R(x, t, u(x, t)) = -\gamma u(x, t)$ and boundary conditions (2.1.1) over [0; L] and applying the Laplace transform, we obtain the following equation for the Laplace image $\overline{u}$:

$$(p + \gamma) \int_0^L \overline{u}\,(x, p)\, \mathrm{d}x = \frac{q}{p} + \int_0^L \varphi(x)\, \mathrm{d}x. \tag{2.2.1}$$

After the Laplace transform of the Jeffreys-type equation (2.2.1) and integration of it with (2.1.3), (2.1.4) and (2.1.1), we obtain the following integral condition:

$$\int_0^L \psi(x)\, \mathrm{d}x = q - \gamma \int_0^L \varphi(x)\, \mathrm{d}x, \tag{2.2.2}$$

which means that in general the function $\psi(x)$ cannot be equal to zero within [0; L], since (2.2.2) may not be valid. There is a different way to obtain (2.2.2) by integration of (1.3) over [0; L], assuming $t = 0$ and substituting the initial conditions (2.1.2). Therefore, (2.2.2) implies the mass conservation at the initial time moment.

## 2.3 Model for dynamics of *gap* gene proteins concentration

To define the reaction term $R(x, t, u(x, t))$ in (1.5) a synthesis function $g(\eta(x, t))$ was introduced (see Mjolsness *et al.*, 1991), which takes into account that upstream segmentation genes (e.g. *maternal* genes) regulates the expression of downstream genes (e.g. *gap* genes) and interactions between the *gap* genes in the gene network. Furthermore, the *gap* genes are supposed to degrade uniformly with constant rate, that leads to $R(x, t, u(x, t)) = -\gamma u(x, t) + g(\eta(x, t))$, and therefore (1.5) can be written as:

$$\mathfrak{L} u(x, t) - \beta u(x, t) = \chi g(\eta(x, t)) + \varepsilon g_t(\eta(x, t)). \tag{2.3.1}$$

Therefore, the dynamics of protein concentrations in the gene network consisting of four *gap* genes is described formally by means of the Jeffreys-type equations together with boundary conditions and initial conditions:

$$\begin{gathered} \mathfrak{L}^{(i)} u^{(i)} - \beta^{(i)} u^{(i)} = \chi^{(i)} g^{(i)}(\eta^{(i)}) + \varepsilon^{(i)} g_t^{(i)}(\eta^{(i)}), \\ u^{(i)}|_{t=0} = \varphi^{(i)}(x),\; u_t^{(i)}|_{t=0} = \psi^{(i)}(x), \\ u_x^{(i)}|_{x=0} = \varphi_x^{(i)}(0) \exp\left(\frac{t\,\alpha^{(i)}}{\delta^{(i)}}\right), \end{gathered} \tag{2.3.2}$$

$$u_x^{(i)}|_{x=L} = \varphi_x^{(i)}(L) \exp\left(\frac{t\,\alpha^{(i)}}{\delta^{(i)}}\right), \tag{2.3.3}$$

coupled via the non-linear terms $g^{(i)}(\cdot)$, which determine synthesis of protein $i$ and depend on $\eta^{(i)}$, representing a contribution of all factors to regulation of gene $i$ expression. The gene reaction on regulators influence has the threshold behaviour, therefore the synthesis function is assumed to be proportional to the 'sigmoid' curve, and its argument contains the additive contributions of all regulatory factors:

$$\begin{gathered} g^{(i)}(\eta^{(i)}) = \frac{G^{(i)}}{2}\left(1 + \tanh\left(\eta^{(i)}(x, t, u^{(i)})\right)\right), \\ \eta^{(i)}(x, t, u^{(i)}) = \sum_{j=1}^{4} T^{ij} u^{(j)} + \sum_{k=1}^{K} E^{ik} v^{(k)} + f^{(i)}, \end{gathered} \tag{2.3.4}$$

where the constant $G^{(i)}$ denotes the maximum intensity level of gene $i$ protein synthesis, the matrix coefficients $T^{ij}$ characterize the level and type of regulation of gene $i$ protein by other *gap* genes, $E^{ik}$ are the coefficients of regulation by *maternal* genes, which concentrations denoted as $v^k$, and $f^{(i)}$ denotes the contribution by external factors, that is assumed to be homogeneous in space and time. The function $g(\eta(x, t))$ is widely used in *gap* genes expression modelling (see, e.g. Gursky *et al.*, 2004, 2008; Jaeger *et al.*, 2004; Kozlov *et al.*, 2012; Mjolsness *et al.*, 1991; Reinitz *et al.*, 1995).

For numerical simulation, the initial protein concentrations data were taken from the database *FlyEx* (*FlyEx*: Electronic database on segmentation genes expression in *Drosophila*; http://urchin.spbcas.ru/flyex, http://flyex.ams.sunysb.edu/FlyEx), containing experimental data for concentrations of the *Drosophila gap* gene proteins at different stages of development.

Analysis of initial conditions for (2.3.1) is similar to that for (2.1.5). The boundary conditions on $J(x, t)$ are homogeneous, since *gap* genes are expressed inside an embryo, but not at the boundaries. Taking into account the condition:

$$\int_0^L \psi(x)\, \mathrm{d}x = \int_0^L g\left(\eta|_{t=0}\right) \mathrm{d}x - \gamma \int_0^L \varphi(x)\, \mathrm{d}x. \tag{2.3.5}$$

one can guarantee the problem (2.3.2) to be well-posed.

## 2.4 Implementation of numerical simulation method

The system (2.1.2) was solved numerically using the explicit finite difference method in spatial domain (0; 100%) of an embryo length (EL) from $t = 0$ up to 68th minute of development. We used the central difference approximation for $u_t^{(i)}$ and the backward difference approximation for time variable for $u_{xxt}^{(i)}$. The term $g_t^{(i)}(\eta^{(i)})$ was rewritten as:

$$g_t^{(i)}(\eta^{(i)}) = g_{\eta^{(i)}}^{(i)}(\eta^{(i)}) \left(\sum_{j=1}^{4} \eta_{u^{(j)}}^{(i)} u_t^{(j)} + \sum_{k=1}^{K} \eta_{v^{(k)}}^{(i)} v_t^{(k)}\right),$$

and the derivatives $u_t^{(j)}$, $v_t^{(j)}$, $j = \overline{1,4}$ were approximated via the backward differences.

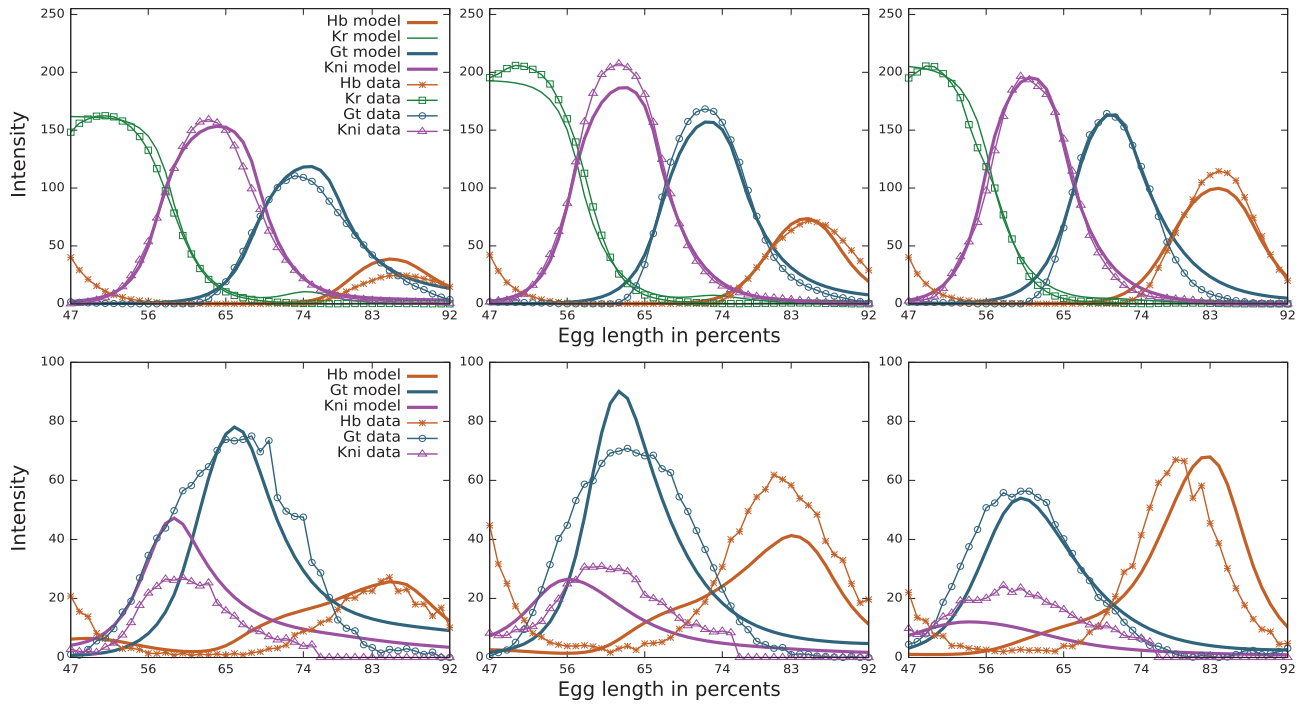



**Fig. 2.** Comparison of the approximate solution to the Jeffreys-type model with data. Protein concentration profiles in the wild-type embryo are shown in three upper graphs, while three lower graphs illustrate the concentration profiles in the $Kr^{-}$ mutant. Calculations were performed on the whole EL with the Neumann boundary conditions on protein concentrations, while the numerical solution was fitted to the experimental data in the restricted spatial domain [47%; 92%] of EL. Concentration profiles are presented for the time classes 3, 5, 7 in the cycle 14A. Color version of this figure is available at *Bioinformatics* online

We used the spatial step equal to 1% of EL, and the time step was chosen so that the scheme, written for the linear part of the equations in (2.3.2):

$$\varepsilon^{(i)}\, u_{tt}^{(i)} + u_t^{(i)} + \delta^{(i)}\, u_{xxt} - \alpha^{(i)}\, u_{xx} - \beta^{(i)} u = 0,$$

will be spectrally stable. The following stability estimate was obtained:

$$\theta \leq -\frac{4\varepsilon^{(i)}\, h^2\, (\alpha^{(i)} - \beta^{(i)})}{\alpha^{(i)}\, \delta^{(i)}}. \qquad (2.4.1)$$

Details of calculations using this finite difference scheme can be found in Supplementary notes, available online.

## 3 Results

We compared the results of numerical simulation in the framework of the new model based on the coupled Jeffreys-type equations (2.3.2) with the experimental data from the *FlyEx* database in the bounded region (from 47 to 92% of EL) along the anterior-posterior (AP) axis. The model parameters were obtained via fitting the numerical solution to data. The value of residual mean square (RMS):

$$\mathrm{RMS} = \sqrt{(1/N)\sum_{n,i,k}\left(u_n^{(i)}(t_k)_{\mathrm{num}} - u_n^{(i)}(t_k)_{\mathrm{data}}\right)^2} \qquad (3.1)$$

was used for the evaluation of the solution quality. Each difference in (3.1) was calculated between the numerical solution $u_{\mathrm{num}}$ and the experimental data $u_{\mathrm{data}}$ for concentrations, and summation was performed over all nuclei $n$, proteins $i$ and time moments $t_k$, for which the experimental data are available. The expression patterns were estimated also visually by biologists.

We decided to obtain one and the same parameter set suitable for fitting the experimental data for both the wild-type embryo and the mutant in gene *Kruppel* ($Kr^{-}$) simultaneously. To do so, we performed the numerical simulation to model an embryo development during 68 min of cycle 14 for two different genotypes. The spatial distributions of *gap* genes proteins concentrations in comparison with the experimental data for each gene at time classes 3, 5 and 7 in the division cycle 14A is shown in Figures 2 and 3.

The first set of 10 calculations was performed in the *whole* domain (0%; 100%) with the Neumann boundary conditions, while the parameters were found in such a way, that the approximate solution fits the experimental data only in *truncated* domain (47%; 92%) of EL. One of the reasons of narrowing of the fitting region is that an embryo has nearly an ellipsoidal form, and, therefore, the whole EL interval (0%; 100%) cannot be in a microscope focus at the same time. As a result, the data near the ends of the AP axis both in wild-type embryos and in the $Kr^{-}$ mutants seems to be unreliable. Moreover, our computations show unsatisfactory results when fitting region was equal to (35%; 92%) of EL. The failure may be explained, in particular, by that the *gap* genes have different cross-regulatory actions in the AP parts, consequently, representation of the regulators action on their targets along the whole AP interval via one and the same parameter $T^{ij}$ is simple, but not sufficient to describe gene expression in details (Kozlov *et al.*, 2012). Among 10 calculations the best value of RMS was RMS = 8.502. The obtained values of the regulation matrix coefficients are presented in Table 1.

The second set of 10 calculations was performed and the approximate solution was fitted in the region (47%; 92%) of EL with the Dirichlet boundary conditions. The FlyEx database contains the values of protein concentrations only in certain discrete time

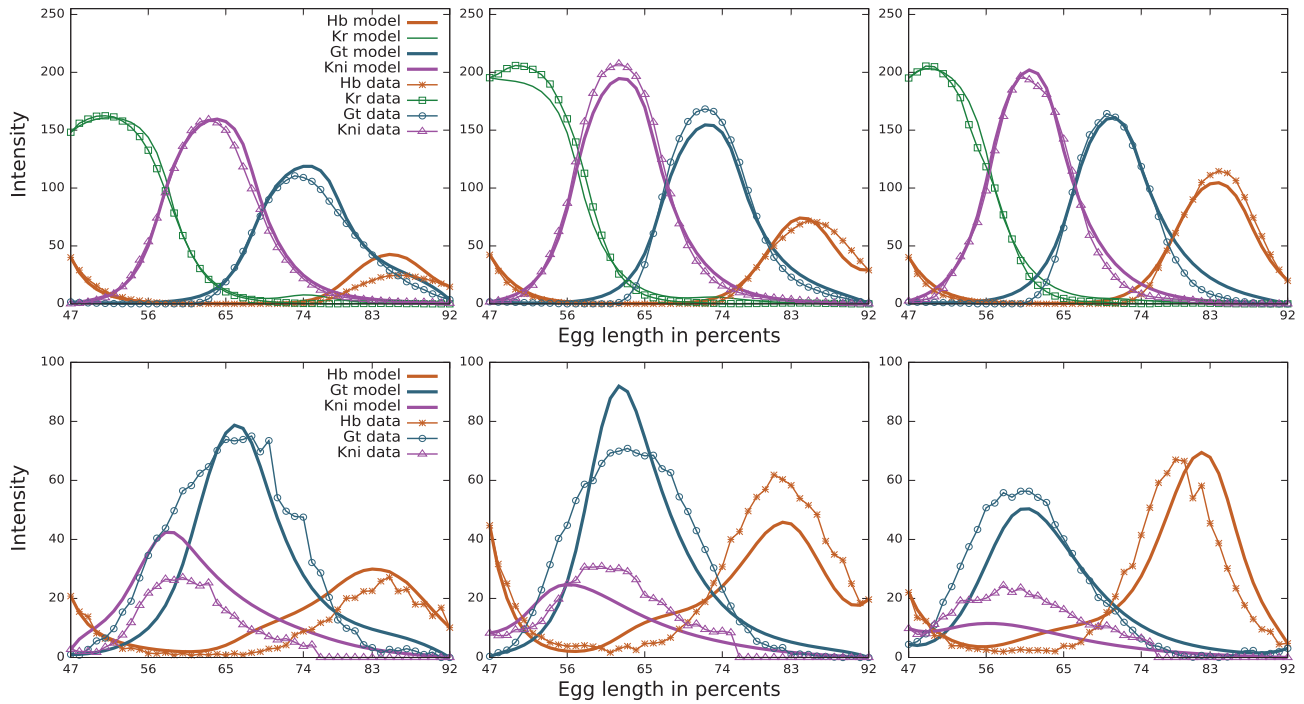



**Fig. 3.** Graphs arranged as in Figure 2 for both calculations and fitting performed in the restricted spatial domain [47%; 92%] of EL with the Dirichlet boundary conditions on protein concentrations for the time classes 3, 5, 7 in the cycle 14A. Color version of this figure is available at *Bioinformatics* online

**Table 1.** The interaction coefficients $T^{ij}$, $i, j = \overline{1,4}$ between *gap* genes and coefficients $E^{ik}$, $i = \overline{1,4}$, $k = \overline{1,3}$ of regulation of *gap* genes by proteins of *maternal* genes for the model with the Neumann boundary conditions

| | hb | Kr | Gt | Kni | bcd | cad | tll |
|---|---|---|---|---|---|---|---|
| *hb* | **0.029** | −0.273 | **0.017** | −0.078 | **0.014** | **0.023** | 0.000 |
| *Kr* | −0.120 | **0.040** | **0.007** | −0.030 | **0.141** | **0.019** | −0.051 |
| *Gt* | −0.172 | −0.064 | **0.032** | −0.006 | **0.001** | **0.026** | **0.002** |
| *Kni* | −0.116 | −0.012 | −0.051 | **0.034** | **0.022** | **0.028** | −0.003 |

*Note*: Bold text is used for better separation of the positive elements of the regulatory coefficients matrix in this table.

**Table 2.** The interaction coefficients $T^{ij}$, $i, j = \overline{1,4}$ between *gap* genes and coefficients $E^{ik}$, $i = \overline{1,4}$, $k = \overline{1,3}$ of regulation of *gap* genes by proteins of *maternal* genes for the model with the Dirichlet boundary conditions

| | hb | Kr | Gt | Kni | bcd | cad | tll |
|---|---|---|---|---|---|---|---|
| *hb* | **0.030** | −0.283 | **0.016** | −0.061 | **0.012** | **0.021** | −0.002 |
| *Kr* | −0.092 | **0.044** | **0.007** | −0.034 | **0.134** | **0.020** | −0.063 |
| *Gt* | −0.164 | −0.051 | **0.034** | −0.006 | **0.006** | **0.025** | **0.007** |
| *Kni* | −0.141 | −0.012 | −0.066 | **0.030** | **0.030** | **0.029** | −0.041 |

*Note*: Bold text is used for better separation of the positive elements of the regulatory coefficients matrix in this table.

moments, therefore the other boundary values required for the numerical scheme with the Dirichlet boundary conditions were obtained by linear interpolation. These modifications resulted in decrease the value of RMS, and lowest value is RMS = 7.317. Results of modified numerical simulations are presented in Figure 3. The values of the regulation matrix coefficients are presented in Table 2.

## 4 Discussion

An application of the Jeffreys-type third-order non-linear partial differential equation to description of *gap* genes expression was considered. We analyzed also the statement of the initial-boundary problem for the Jeffreys-type equation and obtained the relationship for functions in the initial conditions, necessary for the problem to be well posed.

The results of the first set of 10 calculations demonstrate slightly better quantitative fitting to the experimental data on *gap* gene expression in *Drosophila* blastoderm as compared with the conventional model (1.1) with lowest RMS = 8.502 value for the model with the Jeffreys-type equation and the Neumann boundary conditions, while for the conventional model the lowest value is RMS = 8.532. Therefore we conclude that the numerical solution of the new model fits the experimental data with better accuracy. The obtained values of the regulation matrix coefficients, presented in Table 1, are in good agreement with results of regulation type shown experimentally (for review, see Jaeger, 2011) and with regulation type data presented for conventional diffusion model (see Kozlov *et al.*, 2012).

Graphs in Figure 2 demonstrate qualitatively similar behaviour of concentration profiles as compared with the conventional model, i.e., the experimental concentration profiles in the wild-type embryo are fitted with reliable accuracy, except the expression domain of *hunchback* (*hb*) at the left end of the region. The same problem exists in the $Kr^{-}$ mutant model. Moreover, the expression domain of *Giant* (*Gt*) in the $Kr^{-}$ mutant was narrower, than in experiment, and its maximum was sharper. Finally, the position of *hb* maximum concentration was shifted to the right from the position of experimental concentration maximum, and domain expression of *hb* is spread to left side.

To avoid these disadvantages we performed another set of 10 calculations in the narrowed computational domain (47%; 92%) of

EL with boundary conditions of the Dirichlet type. The lowest RMS = 7.317 demonstrates substantially better fit to experimental data in comparison to the Neumann boundary conditions, therefore we conclude that the Dirichlet boundary conditions provide better results for modelling the *gap* genes expression than the conditions of the Neumann type. The values of the regulation matrix coefficients, presented in Table 1, are also in good agreement with experiments and with results for conventional model, as well as for the model with the Neumann boundary conditions.

From the graphs in Figure 3 it can be seen that the modelled concentration profiles are similar to those for the model with the Neumann boundary conditions in Figure 2. Nevertheless is should be noted that the usage of the Dirichlet boundary conditions allows us to predict the expression of all genes very close to the experimental data near the computational domain boundaries for both genotypes. However, the narrower expression domain of *Gt* protein, its sharp maximum and the shifted *hb* expression maximum in $Kr^{-}$ mutant require further study.

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*Conflict of interest*: none declared.

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