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La modélisation UML de la transduction du signal

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par :

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La modélisation UML de la transduction du signal

Lors de ma présentation orale j'ai très brièvement mentionné aMAZE. Comme je l'avais signalé le modèle présenté repose entièrement sur aMAZE. Je me suis donc penché à posteriori sur celui-ci et je me suis rendu compte que depuis la publication de l'article sur lequel je me suis basé (juin 2003) le **modèle UML de la transduction du signal** avait été intégré dans aMAZE. J'ai donc du changer ma présentation et y intégrer une description de aMAZE.

UML étant un langage dont la but est la modélisation et la conception de logiciels, de nombreux concepts UML ne sont pas utilisés lorsqu'on souhaite modéliser des objets ou des processus biologiques. Toutefois il est étonnant de voir combien ce modèle se prête bien à cette tâche.

L'enjeu majeur de la génétique fonctionnelle est de déterminer la fonction biologique de tous les produits des gènes séquencés. Le développement des techniques a comme conséquence une augmentation rapide de la quantité et de la nature des données disponibles.

Le développement empirique et non coordonné des banques de données rend l'analyse croisé des informations provenant des sources différents quasiment impossible. Pour résoudre ce problème plusieurs projets de modélisation ont vu le jour. Leur but est de proposer un modèle unique, suffisamment modulable afin d'avoir une structure unique quelque soit le champ disciplinaire ou l'objet d'étude. Concrètement, cela pourrait permettre une meilleure collaborations des scientifiques qui travaillent sur le séquençage des génomes, avec ceux qui étudient leur fonction.

Nous allons nous intéresser ici à un modèle de la transduction du signal. Celui-ci est une extension du modèle aMAZE et il est capable de décrire aussi bien des voies métaboliques que des réseaux de régulation ou de transduction du signal.

1/ Un bref aperçu de aMAZE

Le projet aMaze a commencé en 1998 à EBI-EMBL (European Bioinformatics Institute / European Molecular Biology Laboratory) avec le soutien des industriels tels que Zenaca, Aventis, Monsanto. A cause des clauses du contrat la base de données aMAZE n'a pu être rendu accessible au public que depuis le 15 juin 2003.

aMaze est un environnement (WorkBench) pour la représentation, la gestion, l'annotation et l'analyse de l'information sur les réseaux des processus cellulaires tels que la régulation de la transcription, les voies biochimiques, la transduction du signal.

Le principe de aMaze est de définir des règles générales qui associent des '*Entités biologiques*' et des '*Interactions*' dans des réseaux complexes de processus cellulaires.

Le modèle aMAZE est basé sur deux classes fondamentales d'objets: '*BiochemicalEntity*'¹ et '*Interaction*'. La première représente une entité physique (protéine, gène ...). Des propriétés de ces entités, comme par exemple la position du gène sur le chromosome, sont représentées comme des attributs de cet objet. La seconde représente des activités moléculaires qui peuvent être de plusieurs types. Par exemple '*EntityProcessing*' et '*Binding*' sont des '*Interactions*' qui ont des '*BiochemicalEntity*' en entrée et en sortie (ex: réaction chimique, interaction protéine-protéine), alors que '*Control*' est une '*Interaction*' ayant en entrée une '*BiochemicalEntity*' et une autre '*Interaction*' en sortie.

Une troisième classe importante de aMAZE est '*Process*'. Elle représente une collection de '*Interactions*' ou de '*Process*'. Cette organisation permet de reconstruire des représentations graphiques des voies biochimiques en reliant des '*Interactions*' par leur '*inputs*' et '*outputs*'.

Pour lier une activité biologique d'une entité structurale (gène, protéine) en particulier avec un contexte le modèle aMAZE dispose des classes '*Compartment*', subdivisé elle même en '*SubcellularComponent*', '*CellType*', '*Tissue*', '*Organ*', '*SystematicGroup*'. Ainsi un objet '*Process*' peut être lié à une combinaison d'objets de la classe '*Compartment*' de manière à décrire le lieu où il se produit.

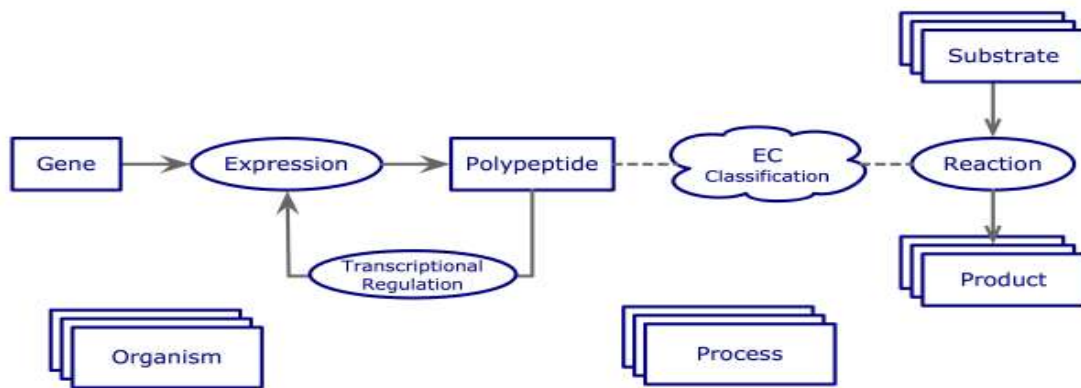
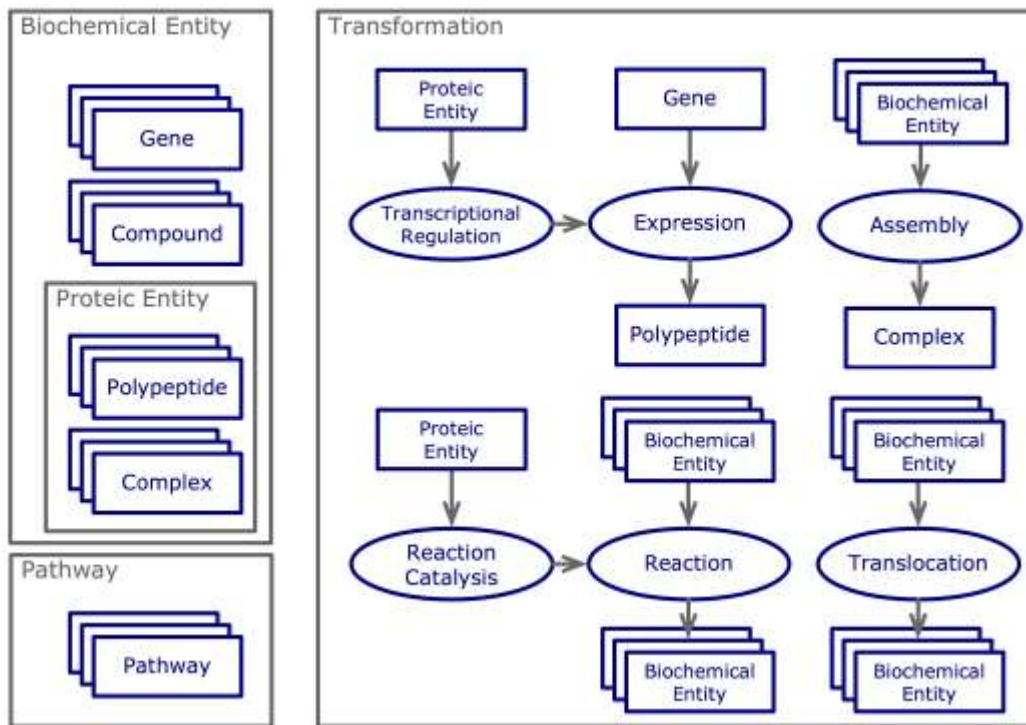


Fig. 1 : Exemple de modélisation d'une voie métabolique dans aMAZE

Fig. 2 : Exemple de modélisation d'une voie de transduction du signal

¹ Les termes utilisés dans les modèles sont laissés en anglais. Le mot anglais est souvent choisi judicieusement pour décrire les concepts relativement abstraits. Une bonne traduction en français demandait une étude particulière dépassant largement mes compétences.

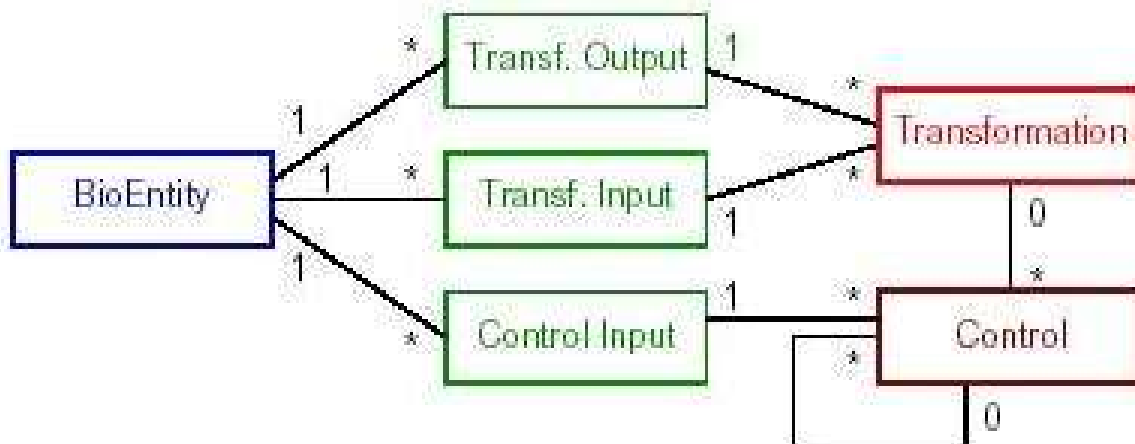


2/ Un modèle objet des voies de transduction du signal

Ce modèle est une extension du modèle aMAZE. Il s'agit donc d'un vrai modèle UML, aMAZE étant juste une modèle pour d'organiser les données dans une base de données et ne respecte pas les spécifications d'UML. Ce modèle peut décrire des voies métaboliques ainsi que des réseaux de régulation de la transcription ou des voies de transduction du signal.

a) Le modèle général

A la base de ce modèle on trouve le schéma suivant:



Toutes les interactions sont des instances de ce schéma. Une réaction chimique, par exemple, est une sous-classe de 'Transformation' et peut avoir plusieurs 'Transf_Inputs' (substrats) et plusieurs 'Transf_Outputs' (produits). Les informations particulières telles

que la stoechiométrie sont des attributs de '*Transf_Output*' ou de '*Transf_Input*', de même que la localisation sub-cellulaire de la transformation. Une '*Transformation*' peut être contrôlé par une autre '*BioEntity*' (ex: catalyse).

b) Le modèle pour le transduction du signal

Les mécanismes de transduction sont particulièrement à l'étude car bien souvent ils jouent un rôle dans la cancérisation des cellules. Comprendre ces mécanismes pourrait amener à proposer de cibles thérapeutiques. Lorsqu'on parle des mécanismes de transduction on entend des voies biochimiques qui transportent une information d'un endroit de la cellule à un autre. Ainsi la fixation d'une molécule messager sur un récepteur membranaire va aboutir suivant une cascade d'événements à l'activation d'un gène dans le noyau. Le produit de ce gène peut lui même être un facteur de transcription, on aboutit ainsi à des réseaux de gènes qui sont coregulés. Pour accroître la complexité de la tâche, une molécule peut ne pas jouer le même rôle selon le tissu où l'organe que l'on étudie. Cette complexité, qui a empoisonné la vie de nombreux étudiants en biologie cellulaire, rend indispensable un modèle pour organiser les connaissances, mais aussi pour aider la réflexion.

Le modèle proposé par l'équipe de Deville & Gilbert repose sur le *modèle général* (a) déjà exposé et qui est utilisé dans aMAZE.

Dans les processus de transduction les éléments suivants sont particulièrement importants :

- la localisation cellulaire de chaque élément
- l'association et la dissociation des complexes protéiques et l'état moléculaire de protéines (ex: phosphorylation, acetylation ...)

La '*Translocation*' est modélisé comme une sous-classe de '*Transformation*', les '*BioEntities*' d'entrée et de sortie sont les mêmes, la localisation initiale est attribut de '*Transf_Input*' et la localisation finale est l'attribut de '*Transf_Output*'.

Une '*Translocation*' peut être contrôlé par un '*TransportFacilitator*', une perméase par exemple.

L'association et le dissociation des complexes protéiques sont modélisées en tant que sous-classes de '*Transformation*' avec des classes spécifiques qui permettent le régulation de ces phénomènes.

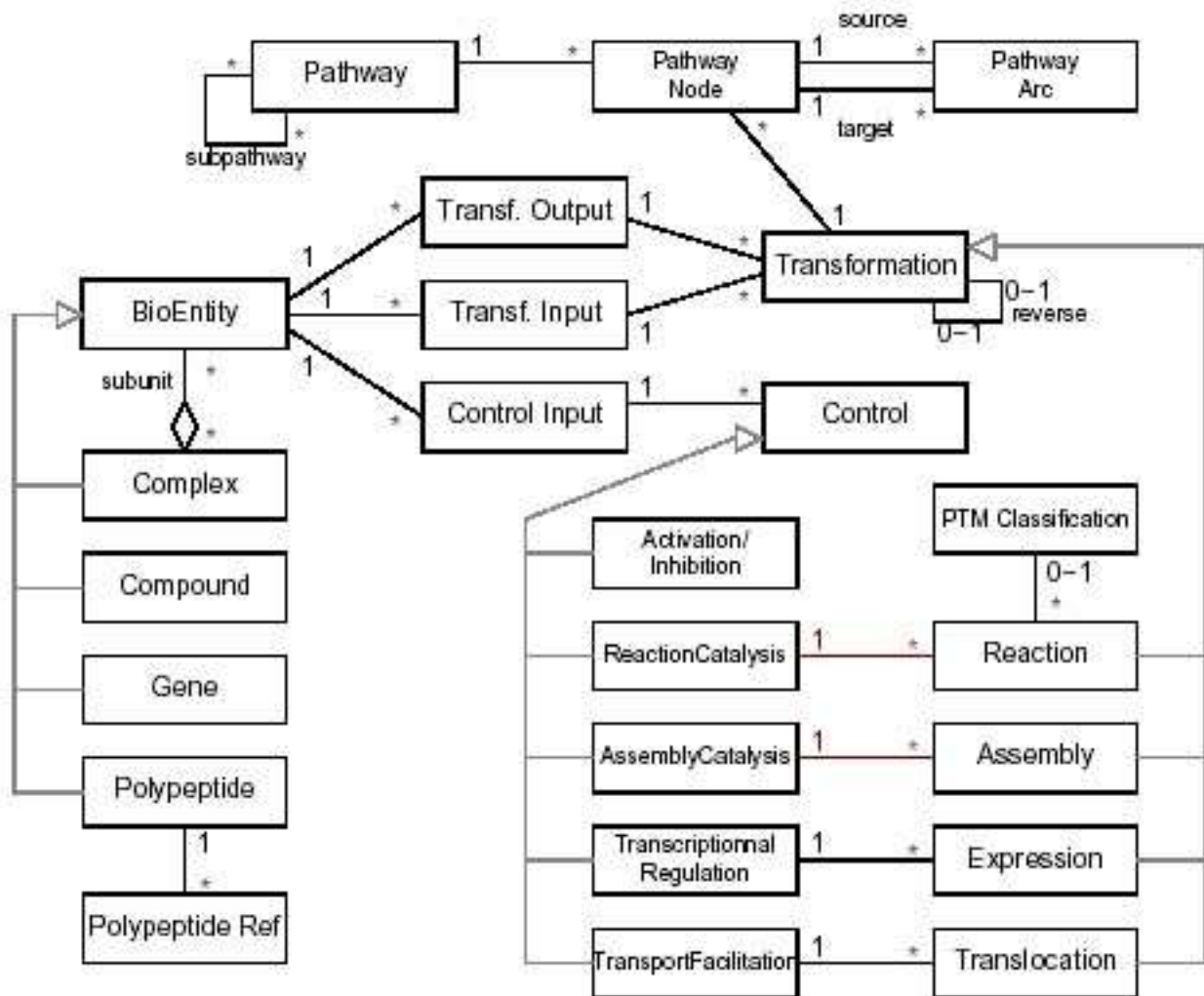


Fig. 2 UML data model for signal transduction

Ce modèle a servi à concevoir un modèle relationnel contenant 30 tables qui ont été implémenté pour MySQL et pour Oracle. Cette base de données a été testé et vient d'être intégrée dans aMAZE. Elle contient actuellement environ 500 *Transformation* et *Control*.

Références:

http://www.info.ucl.ac.be/people/YDE/Papers/eccb03_poster.pdf

<http://www.amaze.ulb.ac.be/>

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